In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 15-1169V
(to be published)

* *	Special Master Corcoran
RAMONA KNORR, *	
Petitioner, *	Filed: December 7, 2018
v. *	Decision; Influenza ("flu") Vaccine; Microscopic Polyangiitis ("MPA"); Granulomatosis with Polyangiitis ("GPA"); Vasculitis
SECRETARY OF HEALTH AND HUMAN SERVICES, *	
Respondent. *	
* *	

Michael McLaren, Black McLaren Jones Ryland & Griffee, Memphis, TN, for Petitioner.

Sarah C. Duncan, U.S. Dep't of Justice, Washington, DC, for Respondent.

DECISION DENYING ENTITLEMENT[1]

On October 9, 2015, Ramona Knorr filed a petition seeking compensation under the National Vaccine Injury Compensation Program ("Vaccine Program").[2] Petitioner alleges that she suffered from several injuries, including hearing loss, microscopic polyangiitis ("MPA") (a form of anti-neutrophil cytoplasmic antibody ("ANCA")-positive vasculitis) with renal failure, and polyneuropathy as a result of receiving doses of the influenza ("flu") vaccine on November 7, 2012, and October 8, 2013, respectively.

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[1] This Decision has been formally designated "to be published," and will be be posted on the Court of Federal Claims's website in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Decision will be available to anyone with access to the internet**. As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the Decision in its present form will be available. *Id*

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3758, codified as amended at 42 U.S.C. §§ 300aa-10 through 34 (2012) [hereinafter "Vaccine Act" or "the Act"]. Individual section references hereafter will be to § 300aa of the Act (but will omit that statutory prefix).

An entitlement hearing was held on October 26-27, 2017. For the reasons stated below, Petitioner has not demonstrated entitlement to compensation under the Vaccine Program. Petitioner's primary theory at hearing – that she began experiencing vaccine-induced symptoms reflective of her vasculitis after the first dose of the flu vaccine in 2012 – relied on establishing that those symptoms were in fact evidence of MPA, but Respondent effectively rebutted such contentions, demonstrating that those symptoms were actually associated with a medically-distinguishable form of vasculitis, granulomatosis with polyangiitis ("GPA"). Petitioner otherwise has not demonstrated with reliable scientific and medical evidence that the second flu vaccine dose she received in 2013 could be, or was, causative of her MPA, especially given the extent to which her expert unpersuasively conflated that form of ANCA-positive vasculitis with GPA.

I. Factual Background

The record in this case consists of Ms. Knorr's medical records, the testimony of multiple experts, and one fact witness, plus the medical or scientific literature submitted by the parties in support of their respective positions. I have reviewed the entire record as required by the Vaccine Act.

November 2012 Flu Vaccination and Subsequent Symptoms

On November 7, 2012, Ms. Knorr received the flu vaccine at the office of her employer, Presbyterian Homes of Tennessee, in Knoxville, Tennessee. Ex. 2 at 20. Prior to this time, it appears that Mr. Knorr was relatively healthy, with no significant issues relevant herein – apart from treatment for fluid in her right ear one year prior on October 17, 2011. Ex. 2 at 8. Earlier records from July 2011 through September 2012 indicated unremarkable physical exams. *See* Ex. 2 at 1-2, 6-7, and 10-17 (detailing normal physical exams from July 2011 through September 2012). Ms. Knorr's records also indicate a past history of attention deficit disorder (including decreased concentration), depression, and stress. Ex. 2 at 6, 8, 11.

Five days post-vaccination, Ms. Knorr presented to her primary care physician ("PCP"), Dr. Raye-Anne Ayo, with complaints of flu-like symptoms (including body aches, sore throat, cough and congestion, nausea, and fever for one to two days). *Id.* Upon exam, Dr. Ayo found that Ms. Knorr had enlarged tonsils and non-tender, enlarged lymph nodes. *Id.* Dr. Ayo also conducted a lab screening for the flu virus, which was negative. *Id.* at 22. Dr. Ayo's overall assessment included flu-like symptoms, and she recommended that Ms. Knorr begin taking Tamiflu. *Id.* Office notes from this visit make no mention of any hearing loss.

Hearing Loss in 2013 and Treatment

On January 19, 2013 (over two months post-vaccination), Ms. Knorr presented to the Minute Clinic in Knoxville, Tennessee, complaining of bilateral ear pain with ear popping, and that she had been experiencing such symptoms for approximately one month (or since the middle of December). Ex. 3 at 1; Ex. 8 at 1-3. Ms. Knorr also complained of postnasal drainage, congestion, and stuffiness. Ex. 8 at 1. Upon exam, her treating nurse practitioner, Mary Anne Webster, noted that she had clear fluid in her left middle ear, and a bulging tympanic membrane in her right ear. *Id.* at 2. The overall assessment included sinusitis and otitis media with effusion, and Nurse Webster prescribed Amoxicillin. *Id.* Following this visit, Ms. Knorr returned to the Minute Clinic roughly two weeks later on February 7, 2013, with continued complaints of bilateral ear pain and nasal congestion. Ex. 3 at 2. Nurse Webster noted that Ms. Knorr now had red eardrums with cloudy fluid on exam, and prescribed Augmentin. Consistent with Ms. Knorr's visit in January, the assessment remained acute otitis media, and included no mention of the flu vaccine as having a connection. *Id.* at 3.

On February 25, 2013, Ms. Knorr took herself to Dr. Bond Almand, an ear, nose, and throat ("ENT") specialist at Blount Memorial Hospital in Maryville, Tennessee. Ex. 3 at 4. During this visit, she reported a gradual, two-month history of hearing loss (with fullness and pressure) that had not improved with antibiotics. *Id.* According to Ms. Knorr, her symptoms included occasional ringing in the ear, as well as occasional pulsing, but no balance issues. *Id.* Upon examination, Dr. Almand found no evidence of any ear infection or ear canal/drum injury, but an audiogram conducted during the visit revealed profound mixed hearing loss in the right ear, and mild to severe hearing loss in the left ear. *Id.* at 4. Dr. Almand's overall assessment also included serous otitis media and asymmetry in bone conduction threshold. *Id.* Following her visit with Dr. Almand, Ms. Knorr presented to Blount Memorial for a follow-up MRI of the brain and ear canals. *Id.* at 6-7. The treating radiologist noted no abnormalities in the brain, but did find "opacification of the majority of the mastoids" in the ears, consistent with a combination of fluid and mucosal thickening. *Id.* at 7.

Ms. Knorr next returned to her PCP, Dr. Ayo, on April 23, 2013, with continued complaints of hearing loss (that she now reported began six months prior "with the flu").[3] Ex. 3 at 8. In particular, Petitioner reported that she continued to experience congestion with general improvement but no resolution, despite multiple rounds of antibiotic treatment. *Id.* Upon examination, Dr. Ayo diagnosed Ms. Knorr with chronic otitis media (consistent with past diagnoses), and chronic rhinitis. *Id.* at 9. Dr. Ayo also found evidence of fluid in the left ear and Eustachian tube dysfunction in her right ear. *Id.* at 8-9. Allergy testing conducted during the visit

[3] Notably, the record does not state whether the "flu" reference pertained to the vaccination or a wild virus infection. *See* Ex. 3 at 8.

was positive for trees, weeds, and mold. These records contain no treater suggestions that the flu vaccine Ms. Knorr received in November 2012 had any relationship with her hearing loss or related symptoms.

Ms. Knorr subsequently presented to Dr. Elise Denneny, a second ENT specialist, on June 6, 2013, at Greater Knoxville Ear Nose & Throat Associates, in Knoxville, Tennessee, with continued complaints of hearing loss in both ears. Ex. 3 at 18. Dr. Denneny's notes reveal that Ms. Knorr reported that she had experienced hearing loss after a "severe upper respiratory tract infection," rather than implicating the November 2012 vaccine. *Id.* at 19. Dr. Denneny observed that Ms. Knorr's audiogram (previously conducted by Dr. Almand) indicated bilateral hearing loss, but her MRI (also conducted by Dr. Almand) showed no abnormalities in the cranial nerves. *Id.* Dr. Denneny's notes also indicated that Ms. Knorr reported "asymmetry in her smile[,]" although the same notes do not set forth any diagnostic analysis of, or treatment recommendation for, this symptom. *Id.* Dr. Denneny recommend that Ms. Knorr schedule a follow-up appointment for placement of tympanostomy tubes[4] to help with her hearing symptoms. *Id.*

Ms. Knorr's next record is from July 2013, and primarily recounts her treatment for seasonal allergies. Ms. Knorr began receiving allergy immunotherapy shots for allergic rhinitis on July 29, 2013, at the Family Health Center in Knoxville, Tennessee. Ex. 3 at 20-26, 31-36. Treatment records indicated that Ms. Knorr received approximately twenty injections during the following two-month period. *Id.* No adverse reactions were noted in the accompanying office notes.

In the interim, Ms. Knorr presented to her PCP, Dr. Ayo, on August 19, 2013, with continued complaints of decreased hearing. Ex. 3 at 23. This record set forth Petitioner's history of hearing loss (via audiogram) and tube placement. *Id.* Ms. Knorr now reported that her tubes had helped with draining fluid from the ears, but she also stated that her hearing loss had otherwise worsened. *Id.* Upon examination, Dr. Ayo found that both ears were "clogged by cerumen[,]" or wax, but her external auditory canals were normal. *Id.* Ms. Knorr's overall assessment continued to include decreased hearing loss and allergic rhinitis, pollen-induced (for which she was receiving allergy shots). *Id.* at 24.

On September 27, 2013, Ms. Knorr presented (for a follow-up) to her ENT, Dr. Denneny at Greater Knoxville Ear Nose & Throat. Ex. 3 at 28. According to this record, Ms. Knorr continued to complain of hearing difficulties plus ear ringing, with onset of symptoms "gradual year(s) ago"

[4] Tympanostomy tubes (or ear tubes) are used to prevent the accumulation of fluid behind the eardrum. Tympanostomy tubes are typically surgically inserted into the eardrum using small, cylinder-shaped tubes made of plastic or metal. See *Tympanostomy Tubes*, Mayo Clinic, https://www.mayoclinic.org/tests-procedures/ear-tubes/multimedia/img-20199962 (last accessed on June 14, 2018).

and no known event preceded her hearing loss. *Id.* During this visit, Ms. Knorr described her current state of hearing loss as "severe and unchanged" (and reported other new symptoms, including ostalgia and light headedness). *Id.* Upon examination, Dr. Denneny noted bilateral gray tympanic membranes in both ears and an occluded tympanostomy tube. *Id.* at 29. Overall, Dr. Denneny's follow-up assessment noted that Ms. Knorr was suffering from chronic serous otitis media, bilateral hearing loss, and allergic rhinitis (consist with her overall health course and statements of past treaters). *Id.* at 30.

October 2013 Flu Vaccine and Subsequent Symptoms

Ms. Knorr received a second flu vaccine on October 8, 2013, at her place of employment, Presbyterian Homes of Tennessee, in Knoxville, Tennessee. Ex. 3 at 37. Specifically, Petitioner was administered Fluarix – an inactivated, quadrivalent (meaning containing four wild flu virus strains), and non-adjuvanted[5] form of flu vaccine. *Id.; see also Package Insert*, FDA, May 2015, filed as Court Ex. 1 (ECF No. 75-1). No adverse reactions were noted the day of vaccination.

Three days later, on October 11, 2013, Ms. Knorr returned to Greater Knoxville Ear Nose & Throat, but this time presented to a different ear, nose, and throat ("ENT") specialist, Dr. Richard Desperio. Ex. 3 at 40. Consistent with her past statements, Ms. Knorr reported (for the second time) a gradual onset of hearing loss beginning "year(s) ago," without reference to any specific prior event (such as vaccination), along with a worsening of symptoms since her last office visit. *Id.* Dr. Desperio's notes indicated that her latest audiogram showed a blocked right tube but no fluid, along with an open left tube. *Id.* at 41. A hearing test returned decreased hearing levels. *Id.* During this visit, Ms. Knorr also reported extreme tightness in her neck and tenderness/pain when opening her mouth. *Id.* Dr. Desperio's overall assessment remained chronic serous otitis media (and also included cervicalgia[6]). *Id.* He advised Ms. Knorr to take Advil or Aleve for her pain, and prescribed Xanax as well. *Id.* Office notes also indicated that Ms. Knorr scheduled a follow-up appointment for six weeks later.

[5] Adjuvants are used in some vaccines to create a stronger immune response to the disease being vaccinated against. *See Adjuvants Help Vaccines Work Better*, CDC, https://www.cdc.gov/vaccinesafety/concerns/adjuvants.html (last accessed on November 20, 2018). Aluminum salts, for example, have been used safely in vaccines since the 1930s. *Id.* Not all vaccines contain adjuvants, however. *Id.* Typical non-adjuvanted vaccines include chickenpox, MMR, rotavirus, seasonal flu, and yellow fever. *Id.*

[6] "Cervical" is a general term used to describe the neck. *Dorland's Illustrated Medical Dictionary* 333 (32nd ed. 2012) (hereinafter *Dorland's*). "Cervicalgia" refers to generalized neck pain. Symptoms can include muscle tightness, spasms, headaches, and decreased ability to move the head. *See Neck Pain*, Mayo Clinic, https://www.mayoclinic.org/diseases-conditions/neck-pain/symptoms-causes/syc-20375581 (last accessed on June 14, 2018).

One week post-vaccination, Mr. Knorr visited her PCP, Dr. Ayo, on October 15, 2013, complaining of a four-day course of flu-like symptoms (including body aches, cough, subjective fever, watery nasal discharge, and sore throat). Ex. 3 at 43. She specifically asserted that her present symptoms were similar to those she experienced following her flu vaccine in November 2012. *Id.* Upon exam, however, Dr. Ayo noted that Ms. Knorr appeared healthy apart from rhinorrhea and general malaise. *Id.* at 44. Her notes also indicated that Ms. Knorr was experiencing temporomandibular joint dysfunction ("TMJ") pain in the jaw and surrounding muscles. *Id.* Her overall impression was that Ms. Knorr's symptoms were flu-like and "seem[ed] related to influenza vaccine." *Id.* Dr. Ayo recommended that Ms. Knorr rest for a week and use a mouth guard for her TMJ pain. *Id.*

On October 22, 2013, Ms. Knorr presented again to Dr. Ayo, now reporting a rash on her neck, chest, and arms for the past week, plus a fever, arthralgia, and a dry cough (for two weeks). Ex. 3 at 45. Dr. Ayo noted that Ms. Knorr received the flu vaccine earlier that month and had reported flu-like symptoms a few days later, but she did not appear to opine as to any causal connection between the vaccine and the present rash. *Id.* Dr. Ayo diagnosed Ms. Knorr with a cough and rash, and prescribed antibiotics. *Id.* at 46. A lab workup conducted during the visit showed increased platelets of 434 (reference range 130-400), but a normal erythematous sedimentation rate ("ESR") of 21 (reference range 0-32), which was not supportive of the conclusion that she was at that time experiencing active inflammation. *Id.* at 51-52.

The lab results from October 2013, however, also revealed the presence of a number of antibodies associated with the Epstein Barr virus ("EBV"). Ex. 3 at 50. Specifically, Petitioner tested positive for Anti-Viral Capsid Antigen ("VCA") IgM antibodies (3.9 on a reference range of 0.0 to 0.8) and IgG antibodies (greater than 8 on the same range), and positive as well for the EBV nuclear antigen ("EBNA") antibody (also greater than 8 on the same range).[7] *Id.* The interpretation chart for this testing classified these results as most likely reflecting that Petitioner was in the convalescent phase of a recent EBV infection (or mononucleosis). *Id.*

[7] Immunoglobulin G (IgG) and Immunoglobulin M (IgM) are antibodies produced in response to infection, and their titer levels can help monitor or detect immune deficiencies. IgM is an indicator of current infection, while IgG reflects exposure to a past infection. Increased levels of IgG or IgM are indicia of hepatic diseases (including connective tissue diseases and acute/chronic infections), while decreased levels are found in patients with primary/secondary immune deficiencies. *See Immunoglobulins (IgG, IgA, and IgM), Serum*, Mayo Clinic Med. Laboratories, https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8156 (last accessed June 14, 2018).

Worsening and Attempts to Diagnose Etiology of Symptoms

Ms. Knorr's condition seemed to worsen in the weeks following her October 22nd appointment. She presented to the emergency room at Parkwest Medical Center in Knoxville, Tennessee, on November 4, 2013, complaining of a rash, fever, and bilateral pain in her upper extremities. Ex. 3 at 54. She specifically recounted at this time that she had received the flu vaccine roughly three weeks prior and developed flu-like symptoms four days post-vaccination. *Id.* Upon intake, the treating physician noted that Ms. Knorr had some weakness, difficulty adducting her thumb, calf pain, headaches, scalp tenderness, and dyspnea upon exertion. *Id.* Ms. Knorr also reported subjective chills and decreased fever, weight loss, and an aching jaw. *Id.* Given her host of symptoms, Mr. Knorr was admitted to Parkwest Hospital from November 4-5, 2013, with concerns for systematic inflammatory response syndrome ("SIRS"), neuralgia, elevated liver function tests ("LFTs"), and a possible vasculitis-type process. *Id.* Initial lab testing conducted during her hospitalization now showed an elevated ESR of 106 (reference range 0-20) – a significant change from the reading obtained two weeks prior - an elevated C-reactive protein of 32.5 (normal 0-0.5), and positive EBV-VCA IgG. *Id.* at 55, 67-69. Additional testing was also notable for a positive p-ANCA antibody titer.[8] *Id.* at 87.

During her stay at Parkwest Hospital, Ms. Knorr was evaluated by an infectious disease physician, Dr. John Adams. Ex. 3 at 57. Dr. Adams observed Ms. Knorr to display generalized weakness, numbness, calf pain, and reduced finger strength upon examination. *Id.* at 57-59. The notes from his examination recount that Ms. Knorr had received a flu vaccine in October, but did not opine as to a possible relationship between the vaccine and her current state. *Id.* at 57. Following the consultation, Dr. Adams assessed Ms. Knorr with a "somewhat unusual syndrome with an apparent initial viral syndrome which could have been Epstein-Barr virus reactivation" followed by abnormal LFTs, although he expressed doubt that she was suffering from an active infection, given her IgG and IgM measurements. *Id.* at 50, 59. Dr. Adams recommended a neurological consultation. *Id.* While he opined that Ms. Knorr was suffering from a "clearly evolving inflammatory process," he was not convinced that her symptoms were related to vasculitis, but more likely some form of acute demyelinating encephalomyelitis (or ADEM). *Id.*

Ms. Knorr was next seen by Dr. James Burns on November 4, 2013, for a neurology consultation. Ex. 3 at 99. Dr. Burns recounted Ms. Knorr's health course, noting that she reported she was in excellent health prior to receiving a flu vaccine the prior year. *Id.* Thereafter, Ms. Knorr

[8] Perinuclear antineutrophil cytoplasmic antibodies ("p-ANCA") are used to evaluate patients suspected of having autoimmune vasculitis (including GPA and MPA). *See Test ID:ANCA*, Mayo Clinic Med. Laboratories, https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/9441 (last accessed on June 14, 2018). P-ANCA antibodies are most closely associated with MPA, however. *See* A. Greco, et al., *Microscopic Polyangiitis: Advances in Diagnostic and Therapeutic Approaches*, 14 Autoimm. Rev. 837, 840 (2015), filed as Ex. C, Tab 2 (ECF No. 19-4).

had developed hearing loss (requiring tympanoplasty tubes) and a Bell's palsy-type appearance following vaccination, along with increased hearing loss following a second flu vaccination in October 2013. *Id.* Similar to Dr. Adam's evaluation, Dr. Burns noted that Ms. Knorr was experiencing hand numbness and weakness (acute onset on day of admission), headaches, aching in the calves/thighs/shoulders, rash, and elevated ESR. *Id.* Following the initial evaluation, Dr. Burns ordered lab testing to measure Ms. Knorr's anti-neutrophil cytoplasmic antibodies (or ANCAs). *Id.* at 101. Ms. Knorr tested positive for p-ANCA antibodies and negative for c-ANCA antibodies. *Id.* at 87. Dr. Burns ultimately raised concerns for the possibility of a vasculitis illness, or a "neurologic reaction to vaccine such as an atypical Guillain-Barre-type presentation." *Id.* at 101. He recommended that Ms. Knorr receive a full neurological evaluation at an alternate facility with the appropriate capabilities. *Id.*

Ms. Knorr was transferred to Fort Sanders Regional Medical Center on November 5, 2013, and remained hospitalized from November 5-12, 2013. Ex. 3 at 112. Upon discharge from Parkwest, her overall assessment included a purpuric, balancing type rash, covering her upper torso, arms, feet, and ankles. *Id.* at 112. The discharging physician indicated that her main neurological abnormalities included decreased adduction of her thumb and index finger, decreased flexion and extension strength in her forearms, as well as hyperflexivity in the upper and lower extremities. *Id.* Lab testing noted in the record upon release indicated abnormal LFTs and elevated platelet and white blood cell counts. *Id.* at 113.

During her stay at Fort Sanders, Ms. Knorr was seen by Dr. Darrell Thomas (a neurologist) on November 5, 2013. Ex. 3 at 119. Dr. Thomas recounted a health history similar to that provided to treaters at Parkwest. More specifically, Dr. Thomas noted that Ms. Knorr had presented to the emergency room at Parkwest with acute onset pain and numbness in her arms and hands (along with general sense of weakness, a rash, and history or hearing loss). *Id.* Upon exam, Dr. Thomas found that Ms. Knorr displayed weakness in her fingers and wrist flexors, but no additional concerning neurological symptoms. *Id.* at 119. Overall, Dr. Thomas assessed Ms. Knorr with dysesthesias and weakness in the upper extremities, and described her condition "to be more of an immune-mediated process probably precipitated by a flu shot." *Id.* He excluded GBS as a possible diagnosis (given Ms. Knorr's normal reflexes and local distribution of weakness), but did not rule out vasculitis or sarcoid. *Id.* Moving forward, Dr. Thomas ordered additional lab testing, an EMG, and a lumbar puncture to test for infection or a carcinomatous-type process.

Ms. Knorr was seen by Dr. Amanda Miller for a rheumatology examination on November 6, 2013. Ex. 3 at 115. Similar to Dr. Thomas's assessment, Dr. Miller indicated that Ms. Knorr had experienced a systematic illness, "possibly a reaction to a flu vaccine, which would be the second severe reaction . . . in two years." *Id.* at 116. Dr. Miller suggested that Ms. Knorr might have some form of vasculitis or other immunologic disease, but was not convinced her symptoms were

autoimmune in nature. *Id.* at 116. Dr. Miller found Ms. Knorr's increased liver enzyme levels (along with elevated platelet counts) to be significant and possibly a marker for an existing inflammatory process. *Id.* Absent any identified infection or other cause (as indicated by Ms. Knorr's labs), Dr. Miller recommended a trial of high-dose steroids. *Id.*

An EMG/NCV conducted on November 7, 2013 was normal with no evidence of neuropathy or plexopathy. Ex. 3 at 144. Spinal fluid studies also revealed no abnormalities. *Id.* Upon discharge, Ms. Knorr's treating physician diagnosed her with "weakness and dysesthesias of the upper extremities following a flu vaccine, suspected inflammatory or autoimmune process." *Id.* at 145. Notes further indicated that "this appear[ed] to be the second serious reaction she has had to flu vaccinations." *Id.* The discharging physician recommended that Ms. Knorr begin therapy for her physical symptoms and prescribed gabapentin. *Id.* at 147.

Vasculitis/MPA Diagnosis

Following her initial hospitalization, Ms. Knorr was seen in the rheumatology clinic at Vanderbilt University Medical Center in Nashville, Tennessee, by Dr. Glenn Douglas on November 19, 2013. Ex. 3 at 161. Ms. Knorr reported a health course similar to those referenced above (including hospitalization for nerve pain and numbness beginning in October 2013). *Id.* Dr. Douglas also included pneumonia, hearing loss, EBV infection, and a rash in her health history. *Id.* Following an evaluation, Dr. Douglas diagnosed Ms. Knorr with ANCA-positive vasculitis with possible renal involvement, as well as polyneuropathy (along with a rash). *Id.* He prescribed Prednisone and Oxycodone (for pain), and recommended that Ms. Knorr schedule a follow-up appointment in two weeks. *Id.*

Petitioner was subsequently hospitalized for vasculitis flares on three additional separate occasions at Vanderbilt Medical Center in Nashville, from November 2013 through January 2014, including: (1) November 27-December 1, 2013; (2) December 3-10, 2013; and (3) January 3-14, 2014. Ex. 3 at 164, 206; Ex. 4 at 27.

On November 27th, Ms. Knorr presented to Vanderbilt Medical Center with a history of ANCA-positive vasculitis (including lower extremity swelling) and complaints of worsening kidney involvement. Ex. 3 at 164. She was monitored and discharged with a diagnosis of lower extremity swelling and blood in stool. *Id.* at 169. Ms. Knorr presented a second time on December 3rd with complaints of shortness of breath and fever related to her vasculitis diagnosis. *Id.* at 206. Upon discharge on December 10, 2013, treating physicians concurred with prior determinations that Ms. Knorr had ANCA-positive vasculitis with possible renal involvement – making the form of vasculitis most likely MPA – and steroid induced-diabetes. *Id.* Following her December 2013 hospitalizations, Ms. Knorr presented a third time to Vanderbilt Medical Center after an

exacerbation of her vasculitis (including symptoms of pain, malaise, blurred vision, and headaches). Ex. 4 at 27. Her diagnoses upon discharge continued to include MPA, renal failure, neuropathic pain, and anemia of chronic disease. *Id.* Treaters recommended that she continue physical therapy, and use Gabapentin and Cymbalta as needed. *Id.* at 28.

Mr. Knorr was hospitalized for a fourth flare-up from March 1-6, 2014, at the University of Tennessee Medical Center in Knoxville, Tennessee. Ex. 4 at 192, 222. Her chief complaint during this visit was fever and generalized weakness (associated with her MPA diagnosis roughly four months prior). *Id.* at 192. Upon examination, the treating physician, Dr. Sahar Lotfi, noted that Ms. Knorr displayed no acute distress (and stated she had been doing well overall), but experienced an onset of lethargy and weakness two days prior. *Id.* Dr. Lotfi opined that Ms. Knorr's symptoms were related to her vasculitis diagnosis, steroid-induced hypoglycemia, and renal failure (as well as the medication she was taking, including Prednisone). *Id.* In light of her renal insufficiency, a right renal biopsy was conducted during her hospitalization which displayed necrotizing and crescentic glomerulonephritis, consistent with ANCA-associated disease. *Id.* at 201, 222, 247. Ms. Knorr's discharge summary indicated diagnoses of MPA, chronic kidney disease, hypertension, and anemia. *Id.* at 222. Dr. Lofti also prescribed Cytoxan for her kidney dysfunction.

Ms. Knorr next presented to a rheumatologist, Dr. Natalie Braggs, at Vanderbilt University Medical Center on March 13, 2014. Ex. 4B at 15. Ms. Knorr recounted her recent diagnoses of MPA and hospitalization for high fever and worsening kidney function. *Id.* Dr. Braggs noted that Ms. Knorr reported that her kidney function had improved with IV Cytoxan. *Id.* According to Ms. Knorr, she was still experiencing pain and numbness in her feet and hands, blurred vision, and occasional shortness of breath (and cough). *Id.* at 15. Dr. Braggs's overall assessment included ANCA-vasculitis, steroid-induced diabetes, and neuropathy. *Id.* at 17. She recommended that Ms. Knorr continue taking Prednisone (decreased to a lower dose), Cytoxan, and Gabapentin, and follow-up as needed. *Id.* Relevant lab testing conducted during a lab follow-up showed a normal C-reactive protein and ESR. Ex. 6 at 25-29.

During the following months, Ms. Knorr saw various additional treating physicians at Vanderbilt Medical Center for follow-up appointments related to her vasculitis diagnosis and kidney dysfunction (as well as additional on-going problems such as steroid-induced diabetes and a vitamin D deficiency). *See, e.g.*, Ex. 4B at 56-57 (4/15/2014 follow-up visit with Dr. William Sullivan), 88 (5/20/2014 follow-up visit with Dr. Sullivan), 180 (6/17/2014 follow-up with Dr. Williams). The records from these visits suggest that Ms. Knorr's condition has seen steady improvement with proper treatment and medication. *See, e.g.*, Ex. 4B at 56, 87. Ms. Knorr has continued to attend physical therapy for her hand/arm weakness. *Id.* at 118, 160; Ex. 6 at 2, 17-55.

II. Fact Witness Testimony

A. Ms. Ramona Knorr

Petitioner testified at hearing. Tr. at 6-59. Her testimony largely consisted of her own recollections of her overall health history prior to receiving the flu vaccines on November 2012 and October 2013, respectively, as well as describing the symptoms that followed.

Ms. Knorr began by describing her overall condition prior to receiving her initial flu vaccine in November 2012. At that time, she was extremely healthy, with no adverse health problems or chronic ailments. Tr. at 12-13. She testified that she worked full-time as an occupational therapist, attended school part-time, exercised occasionally, and cared for her three children. *Id.* at 13.

Next, Ms. Knorr recounted her receipt of the flu vaccine on the day of November 7, 2012. Tr. at 14. She noticed no adverse reaction to the vaccine the day it was administered. *Id.* Following the vaccination, Ms. Knorr stated that she presented to her PCP, Dr. Ayo, four to five days later, complaining of flu-like symptoms (including aches and pains). *Id.* at 15. However, she did not recall experiencing hearing loss at that time. *Id.*

Ms. Knorr recalled going to a Minute Clinic at her local CVS roughly two months post-vaccination, with worsening flu-like symptoms and ear pain/popping. Tr. at 16. Although she categorized her symptoms as gradually increasing over the past months, she testified that she did not return to her PCP or any other physician in the interim due to her busy schedule. *Id.* According to Ms. Knorr, during this visit, she reported her hearing loss began shortly after her initial presentation to Dr. Ayo on November 12, 2012 (likely around November 23rd-25th). *Id.* at 18.

Ms. Knorr expressed frustration that her hearing problems seemed to be getting worse, despite her attempts to cure them (including antibiotics, and tube placement). Tr. at 19, 29-30. She next recalled various appointments for hearing problems beginning in February 2013. Ms. Knorr began with a February 2013 appointment with her ENT, Dr. Almand. *Id.* at 21. According to the medical records, Ms. Knorr told Dr. Almand at this time that her symptoms began two-months (or a "few" months) prior to her visit (which would place onset post-vaccination in December 2012). *Id.* at 22-23. However, Petitioner characterized such statements to Dr. Almand as no more than vague estimations. *Id.* at 23.

Ms. Knorr also discussed an appointment with a second ENT, Dr. Denneny, whose notes indicated that her hearing loss symptoms actually began in June 2012 (pre-vaccination), and/or

followed a URI. Tr. at 32. Ms. Knorr disputed the accuracy of this record, but acknowledged that statements concerning the URI were correct (which, according to Ms. Knorr, would place onset in late November 2012). *Id.* Overall, despite the varying statements concerning the onset of hearing problems, Ms. Knorr continued to maintain that her symptoms began in November 2012, a few weeks following her initial flu vaccine on November 7th. *Id.* at 24.

By the summer of 2013, Ms. Knorr testified, she was having trouble working and keeping up with her graduate school classes. Tr. at 26. She also recalled having an issue with her smile, which she described as "like a Bell's palsy sort of situation" or a "droopy smile." *Id.* at 33, 34. Despite these symptoms, no diagnosis of Bell's palsy (or any other) was ever made, and Ms. Knorr testified that these symptoms resolved on their own. *Id.* at 34.

Ms. Knorr next recalled her general health course following the October 2013 vaccination. Tr. at 36. She presented to her PCP, Dr. Ayo, seven days post-vaccination with complaints of flu-like symptoms (similar to her complaints with regard to her initial flu vaccination in November 2012. Ms. Knorr testified that Dr. Ayo prescribed Tamiflu and recommended that she get some rest. *Id.* She was later diagnosed with Epstein Barr (or mono) in early November 2013 (although she also noted she was diagnosed with mono as a teenager and did not feel as if she was experiencing similar symptoms). *Id.* at 39. According to Ms. Knorr, her health course thereafter continued to deteriorate during the following months, and she could no longer work. *Id.* at 38-39.

Finally, Ms. Knorr recounted her hospitalization for what now appears to be the early manifestations of MPA. Ms. Knorr described her hospital course as "really, really rough." Tr. at 43. She was in and out of Vanderbilt Hospital for four months with various symptomology and flare-ups of MPA. Ms. Knorr testified that these flares ranged in severity and included symptoms such as double vision, headaches, pain, and an inability to walk. *Id.* at 44. She also experienced paralysis in her right hand, hair loss, and Prednisone-induced diabetes. *Id.* at 44, 46. According to Ms. Knorr, her treatment course during this time included plasmapheresis, chemotherapy, spinal taps, and rehab therapy. *Id.* at 44-45. To date, Ms. Knorr continues to have trouble walking, has decreased sensation in her right hand, as well as balance issues and decreased fine motor skills. *Id.* at 50-53. Ms. Knorr testified that she has not returned to work (given the general physical demands), and continues to take azathioprine (immunosuppressant) and gabapentin (for nerve pain). *Id.* at 48-50.

B. Petitioner's Expert – Dr. Eric Gershwin

Dr. Gershwin is an immunologist who testified on behalf of Petitioner and offered three expert reports in the case. Tr. 64-124, 156-58; Ex. 19, dated Feb. 17, 2016 (ECF No. 41) ("Gershwin First Rep."); Ex. 67, dated Aug. 11, 2016 (ECF No. 24-1) ("Gershwin Second Rep.");

Ex. 96, dated Aug. 11, 2017 (ECF No. 42-1) ("Gershwin Third Rep."). Dr. Gershwin opined that Ms. Knorr's initial flu vaccine in November 2012 (resulting in flu-like symptoms, hearing loss, and Bell's palsy-type symptoms), coupled with the second flu vaccine in October 2013 (exacerbating her hearing loss and resulting in additional flu-like symptoms), caused her MPA vasculitis. Tr. at 93, 111, 153.

Dr. Gershwin received his bachelor's degree from Syracuse University in Syracuse, New York, followed by his medical degree, which was completed at Stanford University in Stanford, California. Ex. 66 at 1 (ECF No. 41) ("Gershwin CV"). He then completed his internship and residency at Tufts–New England Medical Center in Boston, Massachusetts. *Id.* at 2. After completing a fellowship in immunology with the National Institute of Health, Dr. Gershwin became an assistant Professor in Rheumatology and Allergy at the University of California, School of Medicine in Davis, California. *Id.* at 2. Along with maintaining a clinical practice, Dr. Gershwin remains employed by the University of California, School of Medicine in Davis, California as the Chief of the Division of Rheumatology/Allergy and Clinical Immunology. Gershwin CV at 1-2; Tr. at 65. He currently serves as the editor-in-chief of the Journal of Autoimmunity as well as several other publications focusing on autoimmunity. Tr. at 80; Gershwin CV at 5. Dr. Gershwin also maintains a clinical practice (one day per week) at UC Davis and spends four to six weeks conducting a rheumatology consult service. Tr. at 78.

To begin, Dr. Gershwin described vasculitis and provided a brief overview of its relevant presenting symptoms. Tr. at 71. Dr. Gershwin defined vasculitis as "inflammation of the [blood] vessel[s]" or an inflammatory response initiated by some injury. *Id.* at 72, 85. While Dr. Gershwin acknowledged that genetic (or inherited) factors can play a role in its development, he opined that vasculitis *requires* an environmental stimulus. *Id.* at 86. He characterized vasculitis as an all-defining term, given the multiple types in existence, which he asserted differ mainly due to the size of the vessel implicated, the presence of specific autoantibodies, as well as the presenting location in the body (i.e. can be limited to the head and neck, for example, or spread through the body). *Id.* at 72, 100, 102. It can also be associated with various environmental factors, including viral illness or independent diseases such as lupus or rheumatoid arthritis. *Id.*

Dr. Gershwin went on to discuss some of the specific ANCA-associated vasculitis (or "AAV") sub-types (i.e. GPA and MPA), given their relevance in the present matter. Dr. Gershwin defined ANCA-associated vasculitis as "a heterogeneous group of diseases that include the presence of circulating ANCAs." Gershwin First Rep. at 22. ANCAs are implicated in the pathogenesis of AAV, although the process by which these antibodies are formed is not well-understood (with genetic, environmental, or infection related-factors all considered possible triggers). *Id.*; *see* R. Wijngaarden, et al., *Hypotheses on the Etiology of Antineurtrophil Cytoplasmic Autoantibody-Associated Vasculitis: The Cause Is Hidden, but the Result Is Known*,

3 J. Am. Soc. Nephrol. 237, 237 (2008), filed as Ex. 53 (ECF No. 41) ("Wijngaarden"). Wijngaarden discusses in depth some of the identified causes of ANCA-associated vasculitis, including silica exposure, genetic predisposition, bacterial/viral infection (such as parvovirus B19), and certain thyroid drugs. Wijngaarden at 237.

Dr. Gershwin defined Wegener's granulomatosis (more accurately termed GPA) to be a type of vasculitis mediated by a collection of white cells called granulomas[9], or foreign body reactions. Tr. at 72; *see also* Gershwin First Rep. at 22-23. GPA can be both acute (resulting in a rapid onset), or indolent (resulting in a progression of symptoms over time). Tr. at 74-75. Dr. Gershwin saw no reason to distinguish between GPA and Ms. Knorr's MPA diagnosis given the overlapping symptoms (although in so testifying he essentially acknowledged that *some* differences existed), despite filing literature acknowledging expressly that MPA is "*distinguish[able] as a separate* ANCA-associated vasculitis." Wijngaarden at 237 (emphasis added); *see also* Tr. at 308-09. He did, however, acknowledge that Petitioner's MPA diagnosis was medically accurate. Tr. at 74, 298.

For Petitioner's causation theory, Dr. Gershwin maintained that Ms. Knorr's vasculitis was the result of immunological insult to her autonomic nervous system attributable to the flu vaccine, occurring via the biologic mechanism of molecular mimicry and producing an inflammatory response. Gershwin First Rep. at 22; Tr. at 143, 150. Dr. Gershwin described molecular mimicry as an "antigen-specific phenomenon where there is activation of autoreactive B and T cells due to antigen similarity between the host antigen and microbial antigen," involving both amino acid sequences as well as the secondary/tertiary structure of the presenting antigen (in this case, a protein sequence from the flu vaccine). Gershwin First Rep. at 21-22. Antigens in the flu vaccine mimicked self-structures in the body, producing a cross-reaction whereby antibodies produced in response to the vaccine also attack those self-structures, resulting in an autoimmune illness. Tr. at 93-95, 143-44, 150-51. Dr. Gershwin's opinion relied specifically on a lengthy block quote set forth in a single cited item of literature. Gershwin First Rep. at 23 (citing T. Duggal, et al., *Antineutrophil Cytoplasmic Antibody Vasculitis Associated with Influenza Vaccination*, 38 Am. J. Nephrology 174, 176-77 (2013), filed as Ex. 24 (ECF No. 41) ("Duggal")); Tr. at 141.

To bulwark this proposed mechanism, Dr. Gershwin relied on various articles (not specific to vasculitis) discussing molecular mimicry as a possible explanation for how infectious agents can stimulate autoimmunity in an antigen-specific way. *See, e.g.*, D. Wraith, et al., *Vaccination and Autoimmune Disease: What is the Evidence*, 362 Lancet 1659 (2003), filed as Ex. 54 (ECF No. 41); Y. Shoenfeld, et al., *Vaccination and Autoimmune-'Vaccinosis': A Dangerous Liaison?*,

[9] Granulomas are areas of inflammation in the body tissue. *See Granulomatosis with Polyangiitis*, Mayo Clinic, https://www.mayoclinic.org/diseases-conditions/granulomatosis-with-polyangiitis/symptoms-causes/syc-20351088 (last accessed on June 18, 2018).

14 J. Autoimm. 1 (2000), filed as Ex. 55 (ECF No. 41). Dr. Gershwin acknowledged, however, that he could not identify homology (amino acid sequential similarity) between the viral components of the version of the flu vaccine Petitioner received and a protein in the body that would be the target of an autoantibody attack resulting in MPA, nor could he specify *what* component of the vaccine was the antigenic mimic. Tr. at 119, 143, 151. At best, he could only cite to an unspecified "ongoing NIH study" that implicates the importance of protein structure in autoimmune cross-reactions (but did not file this study), and also opined the likely target antigen to be the neutrophil cytoplasmic antigen, since it purportedly had such structural homology with a flu vaccine component (again without filing anything in support). *Id.* at 143-45, 151; Gershwin First Rep. at 22.

Alternatively, Dr. Gershwin proposed that viral RNA protein found in certain formulations of the flu vaccine might contribute to the development of the ANCA autoantibodies. Tr. at 119, 143; Gershwin First Rep. at 23-24; *see* L. Jeffs, et al., *Viral RNA in the Influenza Vaccine May Have Contributed to the Development of ANCA-Associated Vasculitis in a Patient Following Immunization*, Clin. Rheumatol. (2015), doi 10.1007/s10067-015-3073-0, filed as Ex. 30 (ECF No. 41) ("Jeffs I"). Jeffs I is a case control study involving a single patient (compared to eight healthy controls and six ANCA controls) who developed ANCA-associated vasculitis two weeks following receipt of a flu vaccine in Australia. Jeffs I at 1. In it, researchers isolated peripheral blood samples from the fifteen patients and found evidence that the vaccinated index patient had increased levels of PR3-ANCA in his blood, leading researchers to conclude that forms of the flu vaccines also containing viral ribonucleic acid (RNA) might be able to stimulate production of this particular ANCA autoantibody. *Id.* at 1-2, 8. Dr. Gershwin did not establish, however, that Fluarix (the version of the vaccine Ms. Knorr received) is comparable to the tested versions of the flu vaccine in Jeffs I, and Dr. Gershwin acknowledged in any event that he did not put much stock in this mechanistic explanation for how ANCA production could be vaccine-stimulated. Tr. at 143 ("I think it's less likely . . . [t]here is not likely to be much RNA there [in the vaccine], but I just wanted to be complete").

There are other problems with Jeffs I. First, it involved PR3-ANCA, an autoantibody more commonly associated with GPA than MPA. *See, e.g.*, A. Greco, et al., *Microscopic Polyangiitis: Advances in Diagnostic and Therapeutic Approaches*, 14 Autoimm. Rev. 837, 840 (2015), filed as Ex. C, Tab 2 (ECF No. 19-4) ("Greco") (determining "PR3-ANCA usually cause a C-ANCA pattern and are mainly associated with GPA[,]" while myeloperoxidase ANCA ("MPO-ANCA") are associated with MPA); L. Guillevin, et al., *Microscopic Polyangiitis: Clinical Laboratory Findings in Eighty-Five Patients*, 42 Arthritis & Rheumatol. 421, 424, 428 (1999), filed as Ex. 50 (ECF No. 41) ("Guillevin") (31 out of 51 MPA patients evaluated in study tested positive for anti-MPO antibodies, where only 4 out of 51 tested positive for PR3). Second, an article with the same primary author published in the same year as Jeffs I (and filed by Petitioner in this case) cautions

against overreliance on the possible implications of Jeffs I. *See* L. Jeffs, et al., *Randomized Trial Investigating the Safety and Efficacy of Influenza Vaccination in Patients with Antineutrophil Cytoplasmic Antibody-Associated Vasculitis,* 20 Nephrology 343, 345-51 (2015), filed as Exhibit 31 (ECF No. 41) ("Jeffs II"). Jeffs II specifically monitored thirty-one patients who already had ANCA-associated vasculitis and concluded they were not likely to experience a relapse after receipt of the flu vaccine. As part of its control grouping, the Jeffs II authors also analyzed 67 healthy patients and found no evidence that the flu vaccine could trigger the relevant ANCA-associated antibodies necessary for disease onset. *Id.* at 343, 348-49. Since it is the Petitioner's theory that the earlier flu vaccine dose from 2012 played a role in causing her vasculitis after the second dose, Jeffs II not only seems to limit the significance of Jeffs I, but calls into question the entirety of the causation theory.[10]

In addition to molecular mimicry, Dr. Gershwin also suggested that the mechanism of bystander activation could play a role in instigating an ANCA-associated vasculitis. As he proposed, bystander activation results "in a release of previously sequestered self-antigens or stimulat[ed] . . . innate immune response." Gershwin First Rep. at 23; Tr. at 142. Dr. Gershwin's first report seems to define bystander activation (or what he also termed "polyclonal activation" at hearing) as an immune mechanism initiated by a vaccine (or viral infection) which results in the activation of T cells apart from any specific antigen stimulation directly caused by vaccination. Gershwin First Rep. at 23; Tr. at 135, 149.

The literature ostensibly supporting this proposition, however, did not explain how bystander activation could act as the predominant driver of an autoimmune process (as opposed to a secondary process fueling an *existing* autoimmune reaction instigated by something else). *See* M. Moro, et al., *A Population Based Cohort Study to Assess the Safety of Pandemic Influenza Vaccine Focetria in Emilia-Romagna, Italy—Part Two*, 31 Vaccine 1438 (2013), filed as Ex. 35 (ECF No. 41); B. Ormen, et al., *Attitudes and Side Effects Related to Pandemic Influenza A (H1N1) Vaccination in Healthcare Personnel*, 46 Mikrobiyol Bul. 57 (2012), filed as Ex. 36 (ECF No. 41) (filed in Turkish language with English abstract); H. Reynolds, et al., *A Prospective Observational*

[10] In addition, Jeffs I seems to possibly embrace a vaccine causation theory that has not been found scientifically reliable (to date) in the Vaccine Program. Jeffs I noted that the examined case study reflected "another of the recently proposed concepts of 'Autoimmune/Inflammatory Syndrome Induced by Adjuvants'" or ASIA. Jeffs I at 8. But the ASIA theory (which relies heavily on the proposition that adjuvants in a vaccine can overstimulate the immune system, thereby precipitating an autoimmune reaction) has repeatedly been found to be unpersuasive and/or insufficiently supported by present science to be reliable. *See, e.g., Rowan v. Sec'y of Health & Human Servs.*, No. 10–272V, 2014 WL 7465661 (Fed. Cl. Spec. Mstr. Dec. 8, 2014); *mot. for review den'd*, 2015 WL 3562409 (Fed. Cl. 2015); *D'Angiolini v. Sec'y of Health & Human Servs.*, No 99–578V, 2014 WL 1678145 (Fed. Cl. Spec. Mstr. Mar. 27, 2014), *mot. for review den'd*, 122 Fed. Cl. 86 (2015), *aff'd*, 645 F. App'x 1002 (Fed. Cir. 2016). More importantly, the version of the flu vaccine Petitioner received does *not* contain an adjuvant – rendering ASIA completely irrelevant as a co-explanatory mechanism. Dr. Gershwin himself specifically disavowed any faith in such a theory. Tr. at 141-42 ("I personally do not believe that the adjuvants within a vaccine can cause an autoimmune disease").

Safety Study on MF59 Adjuvanted Cell Culture-Derived Vaccine, Celtura During the A/H1N1 (2009) Influenza Pandemic, 30 Vaccine 6436 (2012), filed as Ex. 39 (ECF No. 41); Tr. at 143. At hearing, Dr. Gershwin acknowledged that an existing autoimmune reaction (or infectious process) must occur *prior* to the initiation of any polyclonal activation, but he did not identify what process (if any) explained Ms. Knorr's experience (unless it is assumed that Dr. Gershwin's invocation of bystander activation relied on his other mechanism of molecular mimicry occurring first). *See* Tr. at 148-49.

Besides offering literature to support his theory, Dr. Gershwin cited reported cases of onset of ANCA-associated vasculitis two to four weeks after receipt of the flu vaccine (and/or a flu wild virus infection). Gershwin First Rep. at 23; Tr. at 112-13; Duggal (two cases of onset of ANCA-associated vasculitis following flu vaccination, but concluding a causal role cannot be confirmed); R. Birck, et al., *ANCA-Associated Vasculitis Following Influenza Vaccination: Causal Association or Mere Coincidence*, 15 J. Clin. Rheumatol. 289-291 (2009), filed as Ex. 21 (ECF No. 41) ("Birck") (reporting three cases of onset of ANCA-associated vasculitis following flu vaccine, but concluding that that it could not be determined if relationship was causal or due simply to chance); B. Spaetgens, et al., *Influenza Vaccination in ANCA-Associated Vasculitis*, 24 Nephrol. Dial. Transplant. 3258-59 (2009), filed as Ex. 44 (ECF No. 41) ("Spaetgens") (case report detailing temporal relapse of ANCA-associated vasculitis following flu vaccination); M. Uji, et al., *Microscopic Polyangiits After Influenza Vaccination*, 44 Intern. Med. 892-96 (2005), filed as Ex. 61 (ECF No. 41) ("Uji") (case report detailing temporal onset of MPA in an 83-year-old patient following flu vaccination); M. Konishi, et al., *A Case of Microscopic Polyangiitis and Giant Cell Arteritis after Influenza Vaccine*, 34 Jpn. J. Clin. Immunol. 154 (2011), filed as Ex. 32 (ECF No. 41) (case report of 67-year-old patient who developed MPA and giant cell arteritis following a flu vaccine); Wijngaarden at 2 (noting possible seasonal association between the flu wild virus and MPA based on three case reports); *see also* T. Kwok, et al., *Two Rare Cases of Retinal Vasculitis Following Vaccination*, 58 Scottish Med. J. E10-E12 (2013), filed as Ex. 34 (ECF No. 41) ("Kwok") (two case report study detailing onset of retinal vasculitis four weeks and two months following flu vaccination).

Dr. Gershwin also noted the existence of reliable literature observing vasculitis relapse following vaccination. *See, e.g.*, J. Cannata, et al., *Reactivation of Vasculitis After Influenza Vaccination*, 283 Br. Med. J. 526 (1981), filed as Ex. 63 (ECF No. 41); A. Kostianovsky, et al., *Immunogenicity and Safety of Seasonal and 2009 Pandemic A/H1N1 Influenza Vaccines for Patients with Autoimmune Diseases: A prospective, Moncentre Trial on 199 Patients*, 30 Clin. Exp. Rheumatol. S83 (2012), filed as Ex. 33 (ECF No. 41) (noting nineteen mild autoimmune disease flares following flu vaccine administration); *but see* Jeffs II (flu vaccine likely safe for existing cases of ANCA-associated vasculitis). He further submitted adverse event reports of spontaneous vasculitis following immunizations across three international databases. *See, e.g.*, P.

Felicetti, et al., *Spontaneous Reports of Vasculitis as an Adverse Event Following Immunization*, 34 Elsevier 6634, 6634-40 (2016), filed as Ex. 20 (ECF No. 41) (cataloging all reports of vasculitis to EV,[11] VAERS,[12] and VigiBase[13] between January 2003 and June 2014). Although Dr. Gershwin categorized vasculitis as an uncommon or rare disease, he maintained that the literature cited above supported a causal connection between the flu vaccine and vasculitis. Tr. at 112-13, 114, 121.

Dr. Gershwin next discussed the nature of autoimmune conditions and autoimmunity generally, given the accepted principle that genetic and environmental factors can trigger autoimmune disorders. Tr. at 94-96. He was unable to identify what specific suspected genetic factors might be relevant to Ms. Knorr (beyond the somewhat conclusory assertion in his first report that she likely had a "unique genetic predisposition"). Gershwin First Rep. at 24. Instead, he emphasized possible environmental factors. Tr. at 96. Thus, given Ms. Knorr's course of symptoms (including hearing loss and Bell's palsy) following the first flu vaccine, and then her worsening hearing loss (and vasculitis diagnosis) following the second, a "striking" association exists between Ms. Knorr's vaccinations and her subsequent disease course. *Id.* at 97.

To bulwark his theory, Dr. Gershwin attempted to provide a close reading of Ms. Knorr's documented health course based upon the filed record. He concurred with her formal MPA vasculitis diagnosis in November 2013, although he did point to a record suggesting a treater expressed concerns about GPA. Tr. at 71, 88, 101, 117, 297; Gershwin Frist Rep. at 21; Ex. 18 at 666. Dr. Gershwin opined that Ms. Knorr experienced flu-like symptoms and hearing loss following her receipt of the flu vaccine in November 2012, with additional flu-like symptoms and a worsening of hearing loss following the second flu vaccine received in October 2013 – in turn leading to the vasculitis diagnosis roughly a month later, in November 2013. Tr. at 89-91. The second vaccine she received in October 2013 was essentially a "booster shot" that amplified her aberrant immunologic reaction (already established as pathogenic in light of the first time she received the flu vaccine), resulting in her "crescendo" of symptoms leading to her November

[11] EudraVigilance ("EV") is the European Medicines Agency ("EMA") management system for reporting adverse reactions to medications and drugs. EMA (along with the reporting system) is maintained by the European Union. The database requires registration to access materials. As of June 15, 2018, the EMA's website is currently under construction (http://www.ema.europa.eu/).

[12] The Vaccine Adverse Event Reporting System ("VAERS") is a national warning system designed to detect safety problems in U.S.-licensed vaccines. *See About VAERS*, VAERS, https://vaers hhs.gov/about html (last visited June 15, 2018). It is managed by both the CDC and the FDA. VAERS monitors and analyzes reports of vaccine related injuries and side effects from both healthcare professionals and individuals.

[13] VigiBase is a World Health Organization (WHO) database used to obtain case safety reports (ICSRs) of suspected adverse effects of medicine, including vaccinations, collected between 1960-2017 from member countries. Currently, 110 contribute to the database. It is maintained by Uppsala Monitoring Centre in Uppsala, Sweden, on behalf of the WHO. See What Is VigiBase?, UPS, https://www.who-umc.org/vigibase/vigibase/ (last accessed on June 15, 2018).

hospitalization and vasculitis diagnosis. *Id.* at 92, 99, 117. Thus, taking her health course as a whole (including her symptoms following both vaccinations), Dr. Gershwin proposed that Ms. Knorr's onset of hearing loss following her first flu vaccine was the initial symptom of vasculitis (given the indolent nature of the disease, its presenting limited location in the head and neck, and its apparent stabilization following the placement of hearing tubes). *Id.* at 91, 115-17.

In support of these contentions, Dr. Gershwin cited a host of articles purporting to show a connection between hearing loss and vasculitis. Gershwin Third Rep. at 2; *see* S. Bakthavachalam, et al., *Hearing Loss in Wegener's Granulomatosis*, 25 Otol. & Neurotol. 833, 833-34 (2004), filed as Ex. 98 (ECF No. 42-3) ("Bakthavachalam") (56 percent of GPA patients in a 36-person study developed documented hearing loss); N. Rasmussen, et al., *Management of the Ear, Nose, and Throat Manifestations of Wegener's Granulomatosis*, 13 Curr. Opin. Rheumatol. 3, 4 (2001), filed as Ex. 99 (ECF No. 42-4) ("Rasmussen") (30 percent of GPA patients in 124-person study developed new deafness); K. Devaney, et al., *Wegener's Granulomatosis of the Head and Neck*, 107 Ann. Otol. Rhinol. 439, 440 (1998), filed as Ex. 100 (ECF No. 42-5) ("Devaney") (ear pain, edema, and hearing deficit are clinical manifestations of GPA); G. Hoffman, et al., *Wegener's Granulomatosis: An Analysis of 158 Patients*, 116 Ann. Intern. Med. 488, 489 (1992), filed as Ex. 101 (ECF No. 42-6) ("Hoffman") (90 percent of GPA patients in a 159-patient study presented with nasal, sinus, tracheal, or ear abnormalities during initial consultation for treatment). Dr. Gershwin relied on the above articles despite the fact that they solely involved Wegener's/GPA (consistent with his view that MPA and GPA were largely congruent for purposes of present analysis).[14]

Dr. Gershwin next discussed Ms. Knorr's symptom progression over time, endeavoring to pinpoint specific clinical evidence for a vaccine-induced vasculitis injury (or an inflammatory process more generally). As mentioned earlier, Dr. Gershwin maintained that Ms. Knorr's November 2012 manifestation of hearing loss (and subsequent treatment with tubes) represented the onset of her vasculitis. Tr. at 129, 152. He disputed the contention (raised by Respondent) that Ms. Knorr's hearing problems were attributable to a bacterial infection. *Id.* at 119, 127, 132; Gershwin Third Rep. at 1. Rather, Dr. Gershwin opined that the medical record did not establish the existence of a bacterial infection at the time (which would be evidenced by severe pain, pus, and the treatment determination to make immediate placement of tubes or employ intensive antibiotics). Tr. at 120.

[14] Notably, one article cited by Dr. Gershwin (seeking to define the typical presenting clinical symptoms of MPA) specifically excluded patients with ear, nose, and throat symptoms from inclusion in the study. *See* L. Guillevin, et al., *Microscopic Polyangiitis*, 42 Arthritis & Rheumatism 421, 422 (1999), filed as Ex. 50 (ECF No. 41).

Dr. Gershwin also mentioned Ms. Knorr's ESR levels taken in October 2013, which he asserted increased four-fold in the time period following her second vaccination and her hospitalization (thereby establishing a rapidly-progressive inflammatory process). Tr. at 107, 120. Although Dr. Gershwin argued that an elevated ESR can be evidence of systematic inflammation, however, he could not explain Ms. Knorr's course of up and down rates (as her October 2013 ESR levels - taken two weeks post-vaccination – were normal, when compared with those taken during her hospitalization in November). *Id.* at 140. He further admitted that proof of an elevated ESR alone could not advance his overall theory. *Id.* at 107. At the same time, Dr. Gershwin asserted that Ms. Knorr's other lab results (like increased platelet levels) lent further support for his overall opinion that Ms. Knorr was experiencing some inflammatory process that could be linked to her vaccination (and earlier onset vasculitis) – even though her initial ESR findings, taken closer-in-time to the second vaccination, were not elevated. *Id.* at 139-140, 155; Gershwin Third Rep. at 1.

In addition, Dr. Gershwin addressed Petitioner's smile asymmetry that a June 2013 record tangentially mentions as occurring in the time between the two vaccinations at issue herein. He proposed that this could have been evidence of Bell's palsy, a form of neuritis or neuropathy of the face (although it was never formally diagnosed as such). Tr. at 92, 97; *see* Ex. 3 at 18, 99; Tr. at 33-34. If so, Dr. Gershwin found this symptom to be an important potential inflammatory marker, and thus an additional indicator of an ongoing vasculitis initiated by her initial receipt of the flu vaccine in November 2012. Tr. at 93.

Besides offering support for his own theory, Dr. Gershwin made efforts to rebut Respondent's proposed alternate explanations for Ms. Knorr's symptoms. Tr. at 104; Gershwin Second Rep. at 1-2. He acknowledged that Ms. Knorr's treaters had included a possible EBV infection as an explanation for her condition in her differential diagnosis in 2013 (given relevant testing as early as October 2013 revealed the presence of some form of EBV infection, as noted by treaters in contemporaneous records). Tr. at 104-05, 300. Dr. Gershwin maintained, however, that these elevated titer levels simply indicated that Ms. Knorr's immune system had *previously* been active against the EBV virus (consistent with her medical record, which revealed she had experienced EBV-mediated mononucleosis earlier in life), rather than that she was experiencing a new infection. *Id.* at 106, 147, 150. Accordingly, any EBV infection she was experiencing had been reactivated by something else – most likely the ongoing autoimmune vasculitis, which Dr. Gershwin maintained had begun the year before – rather than that the reactivated EBV infection was *causing* her vasculitis.

To support this proposition, Dr. Gershwin emphasized literature discussing how EBV-related antibody titer measurements should be clinically interpreted, citing an article released by the Centers for Disease Control (the "CDC"). *See Epstein-Barr Laboratory Testing*, CDC, https://www.cdc.gov/epstein-barr/laboratory-testing.html (last accessed on June 15, 2018), filed

as Ex. 103 (ECF No. 47-1) ("CDC Article"). The CDC Article discussed the lab testing helpful in identifying not only whether a person suffers from an EBV infection, but also *when* the infection may have begun. CDC Article at 1. To do so, it reviewed the different kinds of antibodies that will be observed when an EBV infection exists. VCA IgM antibodies appear early in an active EBV infection but soon disappear, whereas EBNA antibodies are not seen during the acute phase of infection but instead arise slowly, up to two to four months after symptoms onset. *Id.* An individual experiencing a current or ongoing EBV infection should test positive only for anti-VCA antigen antibodies, whereas finding antibodies to *both* anti-VCA IgM and EBNA supports the conclusion that the initiating EBV infection likely occurred several months to years earlier. *Id.* at 2. Because Petitioner's testing revealed the latter, she was more likely than not experiencing a reactivated infection, rather than a new one that could have caused her subsequent vasculitis. Tr. at 300-01. He added that irrespective of these results, no treater ultimately concluded that an EBV infection was causative of her MPA. *Id.* at 135, 299-301, 311, 313.

Moreover, even if Ms. Knorr had been suffering from an intercurrent, recent EBV infection, Dr. Gershwin did not deem that as undermining his theory, because the EBV infection would at best be a secondary stimulus resulting from a pre-existing process initiated by the flu vaccine. Tr. at 103, 135, 148; Gershwin Second Rep. at 1-2. Dr. Gershwin thus characterized EBV as a "polyclonal B cell activator," with the measured antibodies attributable to the autoimmune process he alleged Petitioner was then experiencing. Gershwin Second Rep. at 1-2; Wijngaarden at 241 (concluding there is not much support for a viral trigger for ANCA-associated vasculitis); P. Xu, et al., *Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Associated with Epstein-Barr Virus Infection: A Case Report and Review of the Literature*, 42 Infection 591, 591-92 (2014), filed as Ex. 85 (ECF No. 41) ("Xu"). Xu is a case report discussing the onset of ANCA-associated vasculitis in a sixteen-year-old patient, where initial lab testing indicated a serum positive IgM antibody against EBV, but concluding that more research is required before a causal association could be determined. *Id.* at 594.[15]

Dr. Gershwin also attempted to rebut Respondent's assertion that Ms. Knorr's immunotherapy allergy injections (or any diagnosed allergy for that matter) from the summer of 2013 may have played a role in her development of vasculitis, deeming the concept a "red herring." Tr. at 108, 130, 136, 315-16; Gershwin Second Rep. at 1. In his view, the relevant scientific literature does not support the conclusion that allergy shots play any part in B cell immune system stimulation, despite various submissions by Respondent proposing a possible association. Tr. at

[15] Dr. Gershwin cited additional case reports similarly concluding that a causal relationship between EBV and vasculitis-type diseases has yet to be determined. *See* P. Zoroquiain, et al., *Leukocytoclastic Vasculitis as Early Manifestation of Epstein-Barr Virus-Positive Diffuse Large B-Cell Lymphoma of the Elderly*, 34 Am. J. Dermatopathol. 330 (2012), filed as Ex. 87 (ECF No. 41); M. Yamazaki, et al., *Transient Lupus Anticoagulant Induced by Epstein-Barr Virus Infection*, 2 Blood Coag. Fib. 771 (1991), filed as Ex. 88 (ECF No. 41).

110; *see, e.g.*, A. Linneberg, et al., *Allergen-Specific Immunotherapy and Risk of Autoimmune Disease*, 12 J. Allergy Clin. Iummonol. Pract. 161-67 (2012), filed as Ex. 69 (ECF No. 41) (identifying case reports and concluding evidence to support idea that allergen-specific immunotherapy as a trigger for autoimmune diseases is weak and speculative).[16] On cross, Dr. Gershwin asserted that he was the most qualified of the experts to opine on this particular topic, given his background in allergy medicine. Tr. at 303. Relying on this expertise, he opined that immunotherapy injections are not designed to stimulate the immune system, although he did allow for the possibility that any antigen could itself be a stimulant. *Id.* at 304. Overall, however, he testified that the literature suggests that immunotherapy-induced vasculitis is far too rare to be a persuasive possible explanation for Petitioner's MPA. Gershwin Second Rep. at 1.

Finally, Dr. Gershwin asserted that the onset of Ms. Knorr's symptoms occurred three or four days post-vaccination in November 2012, with it progressing thereafter in accordance with the medical record. Tr. at 121, 125. He deemed her initial hearing loss to be the first manifesting symptom, adding that it did not matter to his theory whether that loss was discovered at the time he alleged or even in the winter of 2013. *Id.* at 306. He stressed, however, that his theory *was* dependent on a finding that the autoimmune process in question began with the 2012 flu vaccine. *Id.* at 153-54 (describing both vaccines as "integral" to his theory).

On rebuttal, Dr. Gershwin spent some time addressing distinctions drawn by Respondent's expert Dr. Oddis between MPA and GPA. In his view, the overlap between the two vasculitis variants overshadowed any clinical or diagnostic differences (and therefore it did not matter if some of the literature he relied upon to associate Ms. Knorr's symptoms to her MPA, like hearing loss, mostly related to GPA). Tr. at 296. He noted as well that some treaters had suggested Petitioner was suffering from GPA/Wegener's, as well as the fact that treatments for either variant would be similar. *Id.* at 297-99; Ex. 18 at 740-42, 769 (internal medicine progress note indicating that rheumatology consult suggested MPA diagnosis, but internist suggested possible Wegener's/GPA given renal laboratory abnormalities, and treated Petitioner the same given similarities in treatment for both diseases).

[16] Similarly, Dr. Gershwin offered a series of case reports concerning immunotherapy-induced vasculitis (indicating the rarity of such a reaction) to bolster his assertions that Ms. Knorr's injections did not causally contribute to her symptoms. *See, e.g.*, M. Branco-Ferreira, et al., *Distal Digital Vasculitis Induced by Specific Immunotherapy*, 53 Allergy 102 (1998), filed as Ex. 71 (ECF No. 41); G. Cabrera, et al., *Digital Vasculitis Following Allergic Desensitization Treatment*, 20 J. Rheumatol. 1970 (1993), filed as Ex. 72 (ECF No. 41); L. Sanchez-Morillas, et al., *Vasculitis During Immunotherapy Treatment in a Patient with Allergy to Cupressus Arizonica*, 33 Allergol. & Immunopathol. 333 (2005), filed as Ex. 75 (ECF No. 41); P. Phanuphak, et al., *Onset of Polyarteritis Nodosa During Allergic Hyposensitization Treatment*, 68 Am. J. Med. 479 (1980), filed as Ex. 81 (ECF No. 41).

C. Respondent's Experts

1. *Dr. Lindsay Whitton*

Respondent's first expert, Dr. Whitton, submitted one written report and testified at hearing, proposing that the flu vaccine has not been shown to cause vasculitis, and therefore could not have caused Petitioner's illness. *See* Whitton Expert Report, dated June 6, 2016, filed as Ex. C (ECF No. 18-3) ("Whitton Rep."); Tr. at 165-242. Dr. Whitton's testimony mostly pertained specifically to Petitioner's causation theory as opposed to the veracity of her diagnosis or its onset, although he did occasionally address the latter points.

Dr. Whitton is currently a professor in the Department of Immunology and Microbial Science at the Scripps Institute in La Jolla, California, and has served in this capacity since 1998. Tr. at 158. He received his medical degree from the University of Glasgow in Scotland. Tr. at 158-59; Whitton CV, filed as Ex. D (ECF No. 18-4) at 1. He also received a Ph.D. in molecular biology from the University of Glasgow. Whitton CV at 1. His practice consists almost exclusively of research related to viral immunology, although he also oversees a graduate student program focused on virology and immunology. Tr. at 160-61. Eighty to ninety percent of his research involves immune system responses to viruses, bacteria, and live virus vaccines. *Id*. He has also served on the editorial board of various academic journals focused on virology. *Id.* at 162. Dr. Whitton currently serves as an editor of *Virology* and has published roughly 35 papers on DNA vaccines. *Id.* Dr. Whitton does not see patients and is not currently licensed to practice medicine in the United States. He does not hold any specialties in disease treatment.

With regard to Petitioner's proffered medical theory, Dr. Whitton admitted that reliable medical literature supports the existence of (rare) vaccine-induced injuries occurring via the biologic mechanism of molecular mimicry. Tr. at 190, 204. However, Dr. Whitton took issue with that mechanism's applicability to this case, since it is so dependent on an adaptive immune response (which typically requires a boosted or adjuvanted vaccine). *Id.* at 191-92. The Fluarix form of the flu vaccine Petitioner received is not adjuvanted, diminishing the likelihood that molecular mimicry would occur at all. *Id.* As a result, Ms. Knorr's reliance on an innate immune-mediated response in this case (Tr. at 126; Gershwin First Rep. at 23) rendered it even less likely that the flu vaccine could have initiated an autoimmune process (even though he later admitted an "adjuvant-free preparation[]" like the flu vaccine is still sufficiently immunogenic to function). *Id.* at 236, 240. Despite his assertions, Dr. Whitton did acknowledge that an innate response "may help facilitate or amplify the adaptive response[,]" although it does not appear that this point altered his opinion in the instant case. *See id.* at 192.

Dr. Whitton was the first expert to note the importance of Petitioner's specific diagnosis. He stated that he agreed with Ms. Knorr's final diagnosis of MPA, but disputed Dr. Gershwin's discussion of her diagnosis as interchangeable with Wegener's granulomatosis (or GPA). Tr. at 166, 214, 241-42; Whitton Rep. at 5-6. Rather, in his view MPA is distinguishable from GPA, given the presence of granulomatous inflammation specific to GPA. Tr. at 241. Head and neck symptoms (as seen in Ms. Knorr's case) are also more common in patients with GPA than MPA, although hearing loss can precede both forms of the disease. *Id.* at 215. Dr. Whitton otherwise agreed with Dr. Gershwin that the course of MPA can be indolent (and eventually progressive), rather than strictly acute, and can be initiated by both genetic and environmental factors. *Id.* at 215. He also agreed that MPA is rare, although he disputed it was as uncommon as Dr. Gershwin seemed to suggest. *Id.* at 206; Whitton Rep. at 9.

Based upon his review of Ms. Knorr's health course, Dr. Whitton asserted that her vasculitis was likely due to an alternate cause, such as a bacterial infection. At hearing, Dr. Whitton also offered various explanations for a viral-induced trigger, including a pre-existing ear infection or a reactivation of an EBV infection. Tr. at 165-70, 184-88; Whitton Rep. at 6. Dr. Whitton further opined that Ms. Knorr's onset of allergies and subsequent immunotherapy injections could have played some role in her eventual MPA diagnosis, although he later admitted her symptoms were not temporally congruent with the expected allergy season. Tr. at 174-75, 213; Whitton Rep. at 7.

To support the above, Dr. Whitton identified specific examples from the medical record. Ms. Knorr reported an onset of hearing loss in January of 2013 (or possibly a few months prior near the end of 2012). Tr. at 165-66. But in Dr. Whitton's reading of the records, Petitioner was likely experiencing a bacterial infection of the middle ear during this time. *Id.* at 167-69, 170; Whitton Rep. at 8, 10. For support, he pointed to records from February 2013, indicating complaints of ear pain, redness/cloudiness in the tympanic membrane, fluid in the ear, and antibiotic treatment. Tr. at 167. The antibiotics she was prescribed likely eradicated the infection, but she subsequently developed noninfectious serous otitis media causing her hearing problems (and resulting the placement of tubes to equalize pressure in the ear). *Id.* at 170. Dr. Whitton also took note of a medical record indicating that Ms. Knorr had been diagnosed with fluid behind the ear pre-vaccination in 2011. *Id.* at 213. Taken together, Dr. Whitton attempted to categorize Ms. Knorr's hearing problems (or infection) as "chronic," despite additional later records indicating unremarkable findings. *Id.*

Moving to the summer of June 2013, Dr. Whitton addressed references to an undiagnosed Bell's palsy-type facial asymmetry. Tr. at 171, 173. In his view, the development of these symptoms (along with the subsequent evidence from October 2013) suggested Ms. Knorr had possibly experienced a "recurrence or reactivation" of an EBV infection she experienced earlier

in life. *Id.* at 172-73, 181-82, 320-324; Whitton Rep. at 6-7, 9; *see* B. Lazarus, et al., *Recent Advances in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis*, 28 Indian J. Neph. 86, 89 (2016) ("Lazarus") (categorizing infections as a "second hit" inducer of autoimmunity in the context of the pathogenesis of AAV). If so, then during such a reactivation, Ms. Knorr would have developed anti-EBV IgM antibodies (which subsequent testing corroborated), making them a plausible trigger for her MPA. Tr. at 188.

For support, Dr. Whitton cited case reports indicating an associative link between the EBV virus and vasculitis, although he admitted he could not say for sure if EBV could actually cause the disease or its relevant subtypes, given the state of the literature (and the speculation inherent to case reports generally). Tr. at 188, 196; G. Teng, et al., *Vasculitis Related to Viral and Other Microbial Agents*, 29 Best. Prac. Res. Clin. Rheumatol. 226, 236-37 (2015), filed as Ex. C, Tab 3 (ECF No. 19-5) ("Teng") (citing case reports); A. Schned, et al., *Fatal Relapse of ANCA-Associated Glomerulonephritis Triggered by Successive Epstein-Barr and Varicella Zoster Virus Infections*, 47 Am. J. Kidney Dis. 915-922 (2005), filed as Ex. C, Tab 8 (ECF No. 20-3) ("Schned") (case report detailing relapse of GPA following EBV infection, but determining that it cannot be stated with certainty that the EBV virus caused the relapse); C. Casiraghi, et al., *Epstein-Barr Virus and Autoimmunity: The Role of a Latent Viral Infection in Multiple Sclerosis and Systematic Lupus Erythematosus Pathogenesis*, 8 Future Virology 173 (2013), filed as Ex. C, Tab 5 (ECF No. 19-7) (attempting to link EBV to the development of autoimmunity, but concluding that there is no clear evidence establishing EBV as a trigger).[17]

In making this argument, Dr. Whitton directly took on Dr. Gershwin's assertions about the significance of Petitioner's EBV antibody titer test results, and whether they revealed her EBV infection to be primary or a secondary/reactivated infection from some time in her prior medical history. Tr. at 184-88, 196; Whitton Rep. at 2, 4, 6-7.[18] Dr. Whitton admitted (as per the CDC Article) that the testing at issue revealing presence of EBV antibodies was consistent with the

[17] Dr. Whitton's report also cited additional case reports acknowledging a possible association between the EBV virus and vasculitis, but ultimately concluding that a causal relationship has yet to be determined. *See* Xu (filed by Petitioner and Respondent); T. Daikeler, et al., *Fever and Increasing cANCA Titre After Kidney and Autologous Stem Cell Transplantation for Wegener's Granulomatosis*, 64 Ann. Rheum. Dis. 646 (2005), filed as Ex. C, Tab 7 (ECF No. 20-2); R. Ranganath et al., *Crescentic Glomerulonephritis and Leucocytoclastic Vasculitis Associated With Acute EBV Infection*, 16 Nephrology 617 (2001), filed as Ex. D (ECF No. 37-1); M. Yamaguchi et al., *Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis Associated With Infectious Mononucleosis Due to Primary Epstein-Barr Virus Infection: Report of Three Cases*, 7 Clin. Kidney J. 45 (2014), filed as Ex. E (ECF No. 37-2).

[18] Dr. Whitton also noted the contradiction between Dr. Gershwin's embrace of bystander activation as a possible mechanism under his causation theory and the actual facts of the case. If, he reasoned, bystander activation explained the autoimmune process that allegedly caused Ms. Knorr's MPA, then the same tests revealing the presence of reactivated EBV antibodies should not have come out negative for the reactivation of *other* infections like cytomegalovirus (a common infection that Ms. Knorr likely would have been exposed to in the past). Tr. at 186-87.

latter, although he maintained that convalescence for EBV can be prolonged (weeks to months), thus allowing for the possibility that the EBV infection had begun sometime in 2013 (even if before that October). Tr. at 217-18; *see* M. Paschale, et al., *Serological Diagnosis of Epstein-Barr Virus Infection: Problems and Solutions*, 12 World J. Virol. 31, 31 (2012), filed as Ex. F (ECF No. 49-1) ("Paschale") (finding that the presence of VCA IgM and VCA IgG without EBNA-1 IgG suggests an acute infection, while the presence of VCA IgG *only* and EBNA-1 IgG without VCA IgM suggests a past infection, and the presence of all three may be detected simultaneously in a recent infection or during a course of reactivation).[19] He otherwise questioned Dr. Gershwin's view that a reactivated EBV viral infection could only induce expansion of pre-existing cells responsible for creating ANCA antibodies (i.e., exacerbate an existing autoimmune process) – it could just as easily directly cause the process in the first place. Tr. at 196.

Dr. Whitton also deemed significant Ms. Knorr's receipt of immunotherapy allergy injections during the summer of 2013, although he admitted that he was "not honestly utterly certain about the composition of the . . . shots." Tr. at 175; *see also* Whitton Rep. at 7. Such allergy shots could be a possible trigger of vasculitis, via an adjuvant contained in the shots, such as alum. Tr. at 175-76. (This argument was later greatly undercut when Dr. Whitton admitted that immunotherapy injections are in fact *not* adjuvanted (Tr. at 249)). Dr. Whitton further disputed Dr. Gershwin's assertion that the injections were at best homeopathic in nature, arguing that they could be dangerous because they involve "antibody-mediated disease," and could result in anaphylaxis. *Id.* at 176-77, 237. In support, Dr. Whitton cited to various case reports purportedly evidencing an association between immunotherapy injections and vasculitis, although he admitted he places little weight on case reports generally. *Id.* at 178; *see, e.g.*, A. Linneberg, et al., *Allergen-Specific Immunotherapy and Risk of Autoimmune Disease*, 12 Curr. Opin. Allergy Clin. Immunol. 635-39 (2012), filed as Ex. C, Tab 10 (ECF No. 20-6) (evidence to support immunotherapy-induced autoimmune diseases is weak and based on case reports).

Overall, Dr. Whitton could not opine for sure what caused Ms. Knorr's vasculitis. Tr. at 207. Rather, he maintained that there were too many confounding factors in her health history to conclude that the flu vaccines caused her injury. *Id.* Regardless, he insisted that Ms. Knorr's

[19] Respondent was later allowed to recall Dr. Whitton to clarify his views on the CDC Article – and specifically its statements about what conclusions could be drawn about the nature of EBV antibody test results. *See generally* Tr. at 320-24. He claimed that these criteria (which Petitioner stressed suggested that the proper reading of her test results revealing the presence of EBV antibodies was that the infection was resolved rather than intercurrent) had been revisited – but in any event that he was not maintaining that Petitioner suffered from a primary/recent infection, but rather that the antibodies had been reactivated due to prior exposure. *Id.*

vasculitis began no earlier than October 2013 (following her second vaccination), although he somewhat revised this view in light of her Bell's palsy-like symptoms, which he opined could indicate onset of symptoms as early as June 2013. *Id.*

2. *Dr. Chester Oddis*

Respondent's second expert, Dr. Oddis, submitted one written report and testified at hearing. Similar to Dr. Whitton, Dr. Oddis proposed that the flu vaccine has not herein been shown to cause Ms. Knorr's vasculitis, but he also offered testimony illuminating the precise nature of Petitioner's illness that bears significantly on my ultimate determination of this case. *See* Oddis Expert Report, dated July 1, 2016, filed as Ex. A (ECF No. 18-1) ("Oddis Rep.").

Dr. Oddis is board-certified in internal medicine and rheumatology Tr. at 250; Oddis CV, filed as Ex. B (ECF No. 18-2) ("Oddis CV"). He is presently a Professor of Medicine in the Division of Rheumatology and Clinical Immunology in the School of Medicine at the University of Pittsburgh. Tr. at 250. He received his undergraduate degree from the University of Pittsburgh and his medical degree from Pennsylvania State University School of Medicine. *Id.* at 251. Dr. Oddis specializes in the treatment of idiopathic inflammatory myopathies. *Id.* at 253-54. He has also directed large clinical myositis trials and published extensively on the topic and its correlation with autoantibodies. *Id.* at 254. In addition to his teaching duties, Dr. Oddis maintains a clinical practice. *Id.* at 252. Dr. Oddis testified that he sees patients at the University of Pittsburgh clinic weekly. *Id.* His clinical practice includes all rheumatologic diseases, including ANCA-vasculitis and MPA. *Id.* at 253. At hearing, he estimated that he has treated roughly 100 patients with ANCA-positive vasculitis (including MPA and GPA). *Id.*

Consistent with Drs. Gershwin and Whitton, Dr. Oddis agreed that Petitioner suffers from MPA vasculitis. Tr. at 259; Oddis Rep. at 4. He did not, however, accept Dr. Gershwin's assertion that MPA and GPA (Wegener's) were interchangeable, given important clinical distinctions between the two, including the presenting antibody and evidence of granulomas in tissue – distinctions born out in Petitioner's presentation (since, as the record establishes above, Petitioner did *not* have the antibodies associated with GPA, nor did she ever display granulomas). Tr. at 259-60, 263.

To illustrate this point, Dr. Oddis embarked on an extended explanation of the distinctions between the two ANCA-associated variants. He characterized MPA as a p-ANCA-antibody disease targeting the myeloperoxidase antigen in the body; GPA, by contrast, is c-ANCA-mediated and targets the proteinase 3 antigen. Tr. at 250, 289. With GPA, moreover, a tissue biopsy would reveal the presence of immune-mediated granulomas, while MPA is not so characterized. *Id.* at 260-61. In addition, MPA typically presents in an "aggressive" and acute fashion, and is not associated with a long progressive course. *Id.* at 289. Finally, while both GPA and MPA can

manifest adverse symptoms related to kidney and respiratory function, ENT dysfunction (including hearing loss) is *rarely* associated with MPA. *Id.* at 261-62, 264, 295. This therefore reduced the significance, in Dr. Oddis's estimation, of the hearing loss evidence in the medical record cited as proof that Petitioner suffered from MPA beginning sometime between the first and second vaccinations (although he acknowledged that such symptoms could be secondary to different forms of vasculitis regardless). *Id.* at 295.

Relying on this diagnostic distinction, Dr. Oddis maintained that Petitioner improperly relied on literature specific to GPA to support her claim (due to the recognized clinical differences between GPA and MPA, particularly with regard to ENT symptoms). *See* Guillevin at 422. Guillevin in particular specifically studied patients with MPA, and in so doing *excluded* GPA patients with ENT symptoms, such as the presence of granulomas in the ear. *Id.* at 291-93. Much of the other literature cited by Dr. Gershwin as establishing a causal connection between vasculitis and hearing loss related to patients diagnosed with GPA (not MPA). Tr. at 268; *see generally* Bakthavachalam; Rasmussen; Hoffman. Ms. Knorr's diagnosis, by contrast, clearly did not include GPA, and the medical record revealed nothing that would support such an alternative diagnosis. Tr. at 269.

Based on a review of Ms. Knorr's health history, Dr. Oddis proposed that her hearing loss likely began in early 2013, and could not be associated with any symptoms relating to her subsequent 2013 MPA diagnosis. Tr. at 264, 267, 282, 295. He described her hearing loss as unilateral, but allowed for the possibility that in some instances it presented as bilateral. *Id.* at 264, 283-84. Although he could not identify a specific cause of this hearing loss, Dr. Oddis opined that the record suggested she likely had some form of an ear infection in early 2013. *Id.* at 266. In addition, Ms. Knorr's treaters diagnosed her with "serous otitis" in 2013, and proceeded as if the otitis were infection-induced, despite a lack of record of evidence of pus or other more obvious indicia of infection. *Id.* at 267, 284-85; Oddis Rep. at 5.

In addition (and consistent with Dr. Whitton's testimony), Dr. Oddis opined that Ms. Knorr's health history included too many intervening factors to conclude that the flu vaccine was casual of her vasculitis injury (such as chronic ear infection, allergies, and the allergy shots treatment). Tr. at 267-68; Oddis Rep. at 5-6. Dr. Oddis specifically expressed concern with the twenty-two immunotherapy injections Ms. Knorr received in the summer of 2013, which he opined could not be discounted as a causal agent. Tr. at 267. Immunotherapy injections may stimulate the immune system "in some fashion or form," although Dr. Oddis later admitted that he could not say what specifically the injections were meant to do. *Id.* at 269, 289. He also acknowledged that he lacked sufficient expertise to opine on the topic. *Id.* at 289. Dr. Oddis did not, however, deem Ms. Knorr's Bell's palsy-type symptoms (facial asymmetry) suggested in a June 2013 record to be of any significance, given the lack of facial nerve involvement with MPA. *Id.* at 270.

With regard to Ms. Knorr's October 2013 symptoms, Dr. Oddis observed the discrepancy between her severe symptomology course and her "rock solid" ESR levels when first measured in October 2013, not long after receipt of the second flu vaccine dose. Tr. at 271; Oddis Rep. at 5-6. According to Dr. Oddis, a normal ESR is inconsistent with a typical MPA course unless the disease process is "better under control." Tr. at 272. As a result, he disputed that her vasculitis could have begun close to the time of her vaccination. *Id.* Rather, he opined that early November 2013 – at which time the record revealed her elevated ESR, coupled with a now "full blown phase" of vasculitis (and pANCA-positive antibodies) – was the more likely onset date. *Id.* When cross-examined, however, Dr. Oddis did allow for the possibility of MPA developing with an initially normal ESR rate. *Id.*

Similar to Dr. Whitton, Dr. Oddis found significant the fact that Ms. Knorr's lab results revealed increased levels of EBV autoantibodies. Tr. at 274. Such results suggested to him that Ms. Knorr had an active EBV infection in October 2013 that also may have played a causal role in her development of MPA. *Id.* Dr. Oddis admitted that the literature cited by Respondent linking an EBV infection to ANCA vasculitis consists mainly of case reports, although he opined that they should be given some weight. *Id.* at 274-75; *see also* Xu. Even so, Dr. Oddis agreed that he lacked the relevant expertise to opine as to an infectious disease alternative cause for Ms. Knorr's injuries, and he also declined to opine on the proper interpretation of the EBV antibody measurements set in the CDC Article. Tr. at 287-88.

Dr. Oddis made some efforts to address the sufficiency of Petitioner's "can cause" showing. Tr. at 275. He testified that he knew of no evidence linking the flu vaccine to ANCA vasculitis, and thus could not accept that the flu vaccine could have caused Ms. Knorr's injuries without more persuasive scientific and clinical evidence. *Id.* He did, however, admit that some reliable literature suggested a seasonal correlation between the timing of flu vaccinations and onset of MPA. *Id.* at 280-81; *see* Wijngaarden at 2. He again reiterated that overall he lacked the expertise to opine on causation. Tr. at 279.

D. Post-Hearing Expert Reports

At my direction, the parties submitted post-hearing expert reports near the end of October 2018, to further clarify an issue I deemed to be inadequately addressed at hearing. In the process of deciding the case, I had become concerned that Petitioner's causation theory (which by Dr. Gershwin's admission relied heavily on linking the two flu vaccines to her MPA, with her intervening ENT symptoms as proof of an initial vasculitis reaction) was deficient. However, the obvious temporal association between the *second* vaccination and Petitioner's MPA still allowed for the possibility that her injuries were vaccine-caused – if the frame for considering her claim were shrunk. I therefore asked them to address whether (and if so, how) the second flu vaccine

Petitioner received in October 2013 could be solely causal of her MPA. *See* Scheduling Order, dated July 19, 2018 (ECF No. 66). Below is a brief summary of the filed responses.

1. *Dr. Gershwin*

Dr. Gershwin filed his supplemental report on August 30, 2018. *See* Post-Hearing Report, dated August 11, 2018, filed as Ex. 104 (ECF No. 69-1) at 2-3 ("Gershwin Supp. Rep."). Assuming (as per my direction) that Ms. Knorr's November 2012 vaccination played *no* role in the developmental of her MPA symptoms, Dr. Gershwin opined that her second flu vaccine (received on October 8, 2013) could alone be the trigger for her MPA.

In so maintaining, Dr. Gershwin again invoked the mechanism of molecular mimicry as the most likely process for induction of Ms. Knorr's MPA, with her symptoms progressing as would be expected for a vaccine-induced reaction based on that process. Gershwin Supp. Rep. at 2. Under the assumed facts, Ms. Knorr's symptom onset following her second vaccination (approximately fourteen days) fell squarely within the timeframe he would expect for an immune insult subsequent to a vaccine reaction, which in his opinion, could occur within thirty days following vaccination. *Id.* at 2. For this conclusion Dr. Gershwin relied heavily on the documented medical record, which he argued showed that Ms. Knorr had presented to treaters with concerns for influenza-type symptoms on the 15th of October, which then progressed to more concerning symptoms (including an increased SED rate and elevated C-reactive protein levels) between October 22nd and her November 4th hospital presentation. *Id.* at 3.

Dr. Gershwin also offered two additional scientific articles in support of his opinion. *See* R. Falk, et al., *Clinical Manifestations and Diagnoses of Granulomatosis with Polyangiitis and Microscopic Polyangiitis*, Uptodate, filed as Ex. 105 (ECF No. 69-2); Y. Cao, et al., *Polymorphism and ANCA Disease Risk in White Populations: A Metaanalysis*, 42 J. Rheumatology 292 (2015), filed as Ex. 106 (ECF No. 69-3). These articles do not address how the flu vaccine can result in an immunologic insult to the autonomic nervous system via Dr. Gershwin's proposed mechanism, however, or otherwise support causation as his prior testimony and reports proposed. Rather, they seem to have been offered to supplement his argument that MPA and GPA are indistinguishable for causation purposes.

Dr. Gershwin also offered a reply supplemental report aimed at further rebutting the alternative cause based theories offered by Respondent's experts (and revisited in their own post-hearing reports). *See* Post-Hearing Report Reply, filed on Oct. 29, 2018 (ECF No. 73-1) ("Gershwin Reply"). Consistent with earlier testimony, Dr. Gershwin again asserted that Ms. Knorr's EBV infection was best categorized as a "reactivation" of a prior resolved infection (resulting from a non-specific activation of the immune system – presumably caused by the flu vaccine). Gershwin Reply at 2. Dr. Gershwin relied on articles previously submitted with his earlier reports, but also cited one new piece of literature. *See* N. Obel, et al., *Serological Findings*

in Patients with Serological Evidence of Reactivated Epstein-Barr Virus Infection, 104 APMIS 424 (1996), filed as Ex. 108 (ECF No. 73-2) (simultaneous positive results for IgM and IgG-EBNA indicates a reactivation of latent EBV infection). He also again opined that Petitioner's immunotherapy injections played no role in her health course given the lack of scientific evidence causally connecting immunotherapy with vasculitis. Gershwin Reply at 1.

2. *Dr. Whitton*

Dr. Whitton's post-hearing report acknowledged that Ms. Knorr's MPA likely began between October and November 2013 (consistent with his earlier reports), but maintained that the October 2013 flu vaccine she received was only temporally related to the onset of her MPA. *See* Post-Hearing Report, filed as Ex. G (ECF No. 71-1) ("Whitton Post-Hearing Rep.").

Dr. Whitton again contended that there is no verifiable scientific support for a causal relationship between flu vaccines and *any* form of vasculitis. Whitton Post-Hearing Rep. at 4. He also repeated his view that Ms. Knorr's prior EBV infection was the more likely cause of her MPA, characterizing the antibody titer test results as reflecting either a "late primary infection" or "reactivation" of latent EBV. *Id.* at 2 (citing Ex. 3 at 50, 52); Paschale at 33. Moreover, Dr. Whitton contented that the above conclusion is strengthened by the existence of case reports associating the EBV virus with the onset of vasculitis (and other autoimmune diseases generally). Whitton Post-Hearing Rep. at 3-4. He cited two case reports in support of EBV-induced vasculitis (both of which had already been filed in the matter). *See generally* R. Ranganath, et al., *Crescentic Glomerulonephritis and Leucocytoclastic Vasculitis Associated with Acute EBV Infection*, 16 Nephrology 617 (2011), filed as Ex. G, Tab 2 (ECF No. 71-3); M. Yamaguchi, et al., *Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis Associated with Infectious Mononucleosis Due to Primary Epstein-Barr Virus Infection: Report of Three Cases*, 7 Clin. Kindney J. 45 (2014), filed as Ex. G, Tab 3 (ECF No. 71-4).

3. *Dr. Oddis*

Respondent filed one final post-hearing report from Dr. Oddis. *See* Post-Hearing Report, filed as Ex. H (ECF No. 71-5). In it, Dr. Oddis opined that flu vaccine Ms. Knorr received in October 2013 played no role in her onset of MPA (either in isolation or in the context of her first vaccination in 2012). *Id.* at 2. Similar to the post-hearing report offered by Dr. Whitton, Dr. Oddis's report attributed Ms. Knorr's MPA to an EBV reactivation or even the multiple immunotherapy injections (received between August and September 2013) as the more likely antecedent triggers. *Id.* In support, Dr. Oddis cited to case reports (previously filed in the matter) revealing an associative link between the EBV virus and onset of vasculitis, and contended that in most cases of ANCA-associated vasculitis, there is no identifiable cause. *Id.* He otherwise asserted that Dr.

Gershwin had provided no additional evidence that the flu vaccine can cause ANCA-associated vasculitis (or did so in this case). *Id.* at 1.

Procedural History

Ms. Knorr filed her Petition on October 9, 2015. Pet. at 1. Almost eight months later, after most records in the case had been filed, on July 8, 2016, Respondent filed his Rule 4(c) report denying that Ms. Knorr was entitled to compensation. ECF No. 17. The Statement of Completion was then filed on February 8, 2016. ECF No. 11.

Thereafter, the parties began filing expert reports. Petitioner filed an initial expert report from Dr. Gershwin on February 19, 2016. ECF No. 41. Respondent filed an initial expert report from Dr. Whitton on June 6, 2016, 2016. ECF No. 18-3. Following a request to supplement the record with additional expert support, Respondent filed a second expert report from Dr. Oddis on July1, 2016 (ECF No. 18-1). Thereafter, Petitioner filed a supplemental report from Dr. Gershwin on August 11, 2016. ECF No. 24-1. Given the issues identified the expert reports, I scheduled this matter for hearing on October 26-27, 2017, to determine entitlement. ECF No. 23. Prior to the hearing, Petitioner filed a second supplemental report by Dr. Gershwin on August 11, 2017. ECF No. 96.

The entitlement hearing was held as scheduled on October 26-27, 2017. That hearing included testimony from the experts identified above (along with testimony from Petitioner). Following the hearing's conclusion, the parties submitted post-hearing briefs on November 29, 2017, and December 6, 2017, respectively. ECF Nos. 56-57. Thereafter, as noted above I contacted the parties and requested that they file supplemental expert reports addressing whether (were I to find that the first flu vaccine dose was *not* causal of Petitioner's MPA) the second dose from October 2013 could be solely causal, and if so how. All experts weighed in on this topic, and the parties also filed brief additional statements explaining their positions. ECF Nos. 72, 74. The matter is ripe for adjudication.

Applicable Law

A. *Petitioner's Overall Burden in Vaccine Program Cases*

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury" – *i.e.*, an injury falling within the Vaccine Injury Table – corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed.

Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).[20] In this case, Petitioner does not assert a Table claim.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a Non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Sec'y of Health & Human Servs.,* 418 F.3d 1274, 1278 (Fed. Cir. 2005): "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1278.

Each of the *Althen* prongs requires a different showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical

[20] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd* 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015) ("[p]lausibility . . . in many cases *may* be enough to satisfy *Althen* prong one" (emphasis in original)), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017). But this does not negate or reduce a petitioner's ultimate burden to establish his overall entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted).[21]

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs*., 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct – that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be

[21] Although decisions like *Contreras* suggest that the burden of proof required to satisfy the first *Althen* prong is less stringent than the other two, there is ample contrary authority for the more straightforward proposition that when considering the first prong, the same preponderance standard used overall is also applied when evaluating if a reliable and plausible causal theory has been established. *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1350 (Fed. Cir. 2010).

weighed against other, contrary evidence also present in the record – including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Dept. of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. *Law Governing Analysis of Fact Evidence*

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Human Servs*., 3 F.3d 415, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records that are created contemporaneously with the events they describe are presumed to be accurate and "complete" (i.e., presenting all relevant information on a patient's

health problems). *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"), *aff'd*, *Rickett v. Sec'y of Health & Human Servs*., 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked propositions that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Human Servs.*, No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Human Servs.*, 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d at 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms.").

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Human Servs*., No. 03-1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony – especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; *see also Murphy v. Sec'y of Health & Human Servs*., 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Human Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Human Servs*., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Human*

Servs., No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *La Londe v. Sec'y of Health & Human Servs*., 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. *Analysis of Expert Testimony*

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs*., 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993). *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial for a (such as the district courts). *Daubert* factors are usually employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable and/or could confuse a jury. In Vaccine Program cases, by contrast, these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs*., 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness and reliability of expert testimony has routinely been upheld. *See, e.g.*, *Snyder*, 88 Fed. Cl. at 742-45. In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 91997)); *see also Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 Fed. App'x 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

D. *Consideration of Medical Literature*

Both parties filed medical and scientific literature in this case – Petitioner a total of over *80 separate articles* - but not every filed item factors into the outcome of this decision. While I have reviewed all of the medical literature submitted in this case, I discuss only those articles that are most relevant to my determination and/or are central to Petitioner's case – just as I have not exhaustively discussed every individual medical record filed. *Moriarty v. Sec'y of Health & Human Servs.*, No. 2015-5072, 2016 WL 1358616, at *5 (Fed. Cir. Apr. 6, 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted); *see also Paterek v. Sec'y of Health & Human Servs.*, 527 F. App'x 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to – and likely undermines – the conclusion that it was not considered").

ANALYSIS

I. Overview of Medical Concepts

Prior to conducting the *Althen* analysis integral to the resolution of Vaccine Act claims, it is necessary to evaluate Petitioner's diagnosis – and the ramifications of it to her claim. There is no dispute that Petitioner was properly diagnosed in the fall of 2013 with MPA, a form of ANCA-

associated vasculitis. Petitioner does *not* have GPA, and has not been shown to have had it at any time relevant to her claim. She did not bear one of the primary indicia of a GPA diagnosis: large-sized granulomas. Tr. at 293. In addition, she tested positive for the p-ANCA antibodies (associated with MPA rather than GPA). Ex. 3 at 87.

In addition to the above, Respondent's expert, Dr. Oddis, was persuasive in demonstrating that there is a meaningful diagnostic distinction between GPA and MPA. Dr. Oddis was the only expert testifying in this case with some demonstrated individual expertise in the relevant disease/illness.[22] He established that MPA is *not* associated with ENT problems to the extent GPA is, just as GPA has other distinct clinical criteria. Dr. Oddis's opinion, moreover, was not only the product of his own experience in the field, but was corroborated in literature filed in this case. *See, e.g.*, Greco at 839 ("[e]ye and ENT manifestations are not considered clinical symptoms of MPA . . . ."). Indeed, *Petitioner's* own literature stressing the significance of ENT symptoms in an ANCA-associated vasculitis diagnosis consistently addressed the GPA variant, and stressed the degree to which such ENT symptoms are associated *only* with GPA. *See, e.g.*, Rasmussen at 8 ("[w]ith the [diagnostic] nomenclature, a clear distinction was made between [MPA and GPA] according to presence (WG)[23] or absence (MPA) of granulomatous involvement of the respiratory tract"); Bakthavachalam; Devaney; Hoffman.

Despite the above, Dr. Gershwin proposed that the distinction between GPA and MPA was irrelevant for purposes of resolving entitlement. I grant his point that the MPA/GPA distinction is not so total that it fully defeats Petitioner's causation theory. Nevertheless, the distinction negatively impacts large aspects of Petitioner's case, as discussed in more detail below.

II. Petitioner Has Not Carried Her Burden of Proof

A. *Petitioner Has Not Established That Her Symptoms Before October 2013 Were More Likely Than Not Related to Her Subsequently-Diagnosed Vasculitis*

[22] By contrast, Dr. Gershwin (despite his demonstrated immunologic credentials) clearly lacks specialized expertise on the subject of vasculitis. Indeed, he has previously been criticized for opining on vasculitis without a sufficient grounding in the subject. *See, e.g., Schoeberlein v. Sec'y of Health & Human Servs.*, No. 14-697V, 2018 WL 945843, at *1 (Fed. Cl. Spec. Mstr. Jan. 11, 2018) ("Dr. Gershwin's relative unfamiliarity with GPA appeared to affect his opinion as he changed/revised/clarified his written reports during his oral testimony. Overall, Dr. Gershwin's presentation and demeanor reduced his credibility."). I have taken into account his points on these topics nevertheless, but I give his assertions on them less weight given his lack of demonstrated training or consistent familiarity with vasculitides generally.

[23] Rasmussen, a 17-year-old article, refers to GPA by its more classic term "Wegener granulomatosis" or WG. Rasmussen at 3.

Based upon my review of the medical record, and in light of the established distinction between MPA and GPA, I do not find that Petitioner successfully established that her demonstrated ENT symptoms (beginning in late 2012 or early 2013, and then recurring throughout 2013 up to the time she received a second flu vaccine dose) were connected to the more acute symptoms she experienced after that second dose, which were ultimately the basis for her MPA diagnosis.

Dr. Oddis's reading of the medical record was persuasive in suggesting that Petitioner's MPA began in late October/early November 2013, and that her prior symptoms were not reasonably associated with that form of vasculitis. In addition, evidence such as the normal ESR that Petitioner first presented with – followed by a much higher, abnormal ESR level from around the time treaters suspected Ms. Knorr suffered from MPA after she tested positive for ANCA antibodies – was consistent with Dr. Oddis's view that MPA commonly presents in an acute but nonprogressive fashion. *See* Tr. at 261-62, 264, 267-69 271-72, 282, 294-95; Oddis Rep. at 5-6. No treater ever diagnosed Petitioner with GPA either (and the record does not suggest that her ENT symptoms would support such a diagnosis, given the absence of relevant clinical criteria such as granulomas or the particular autoantibodies more closely associated with GPA).

There is also a lack of credible evidence that Petitioner's MPA began before October 2013, even if I accept Dr. Gershwin's argument that the chronic ENT symptoms could still be associated with MPA. Dr. Gershwin did not (at least in the context of Ms. Knorr's health history after the November 2012 vaccination) persuasively establish that her ENT symptoms could be deemed evidence of early vasculitis, given his overall lack of specific expertise with the condition coupled with his overreliance on literature describing GPA symptoms. *See, e.g.*, Bakthavachalam; Rasmussen; Devaney; Hoffman.

I acknowledge that the existing record does not clearly establish an etiology for Ms. Knorr's demonstrated persistent hearing and inner ear symptoms,[24] nor did Respondent succeed in offering a persuasive alternative explanation for these symptoms with preponderant evidence.[25]

[24] Both sides also attempted to define as significant the allusion in Petitioner's medical records from June 2013 to a possible Bell's palsy-related symptom occurring between her two vaccinations (Ex. 3 at 18, 99), but neither was persuasive. The one-time reference to a crooked smile is too ambiguous to give it the significance either side urges, and subsequent records do not corroborate it as meaningful to Petitioner's diagnosis. Indeed, Dr. Oddis was persuasive in establishing that such a facial neuropathic symptom would be a presenting clinical feature of MPA. Tr. at 270.

[25] I do not find, however, that the first flu vaccine plausibly explains these symptoms – regardless of whether they were related to her vasculitis or not. Although the record reveals Petitioner experienced flu-like symptoms within a week of vaccination in November 2012, her ENT symptoms did not begin until approximately a month later (based on her report of them starting a month before her January 2013 doctor's visit). Ex. 3 at 1; Ex. 8 at 1-3. The initial post-vaccination symptoms have not persuasively been related to Petitioner's December or January onset of ear infection symptoms. And although infection has not been preponderantly established as an alternative explanation for Petitioner's symptoms, it has not been effectively rebutted by Petitioner either, thus weakening her showing that the vaccine best explains those symptoms. *See, e.g.*, *Parsley v. Sec'y of Health & Human Servs.*, No. 08-781V, 2011 WL

But the disposition of Petitioner's claims does not require Respondent to do so. Rather, to the extent Petitioner's theory depended on linking the two flu vaccines to her MPA, relying on the intervening ENT symptoms to do so, she was tasked (as part of her overall evidentiary burden) with providing a plausible explanation for the linkage – and the explanation she offered did not meet that test. Petitioner did not otherwise establish that the November 2012 flu vaccine could cause her ENT symptoms even if they were *not* related to her subsequent vasculitis (and indeed largely did not attempt to do so). Accordingly, I do not find on this record that Petitioner's theory could succeed based on connecting the prior vaccination to the October 2013 vaccination and subsequent MPA.

B. *Petitioner's First Flu Vaccine Was Not Likely Causal of Her MPA*

As already noted, Petitioner's overall theory relied heavily on associating the November 2012 flu vaccine she received with her subsequent ENT symptoms, which Dr. Gershwin argued evidenced nascent vasculitis. *See, e.g.*, Tr. at 91-92, 99, 115-17, 153; Gershwin Third Rep. at 2. But in so maintaining, he cited literature discussing GPA symptoms. *See, e.g.*, Bakthavachalam at 833-34; Rasmussen at 4; Devaney at 440; Hoffman at 489. In contrast, Respondent persuasively established that such symptoms are not as commonly associated with MPA, Petitioner's actual diagnosis. In addition, the record is unhelpful to Petitioner on this point; testing does not support GPA as an alternative diagnosis for Petitioner, and no treaters ever proposed that her ENT symptoms reflected the onset of Petitioner's vasculitis. At best, treaters speculated (based on what she reported to them) that she had experienced a prior reaction to the flu vaccine that may have recurred in 2013. But such treater views appear to have been the product of reaction to her reported medical history rather than an informed view based on objective proof, like examination or test results.

Accordingly, Petitioner has not established with preponderant evidence that her November 2012 flu vaccine caused her MPA diagnosed a year later.

C. *Petitioner Has Not Preponderantly Established That the October 2013 Flu Vaccine Caused Her MPA*

Because I have determined that Petitioner's initial ENT symptoms were not related to her subsequently-diagnosed MPA,[26] and that the 2012 flu vaccine dose was not otherwise causal of

2463539, at *14 (Fed. Cl. Spec, Mstr. May 27, 2011) (citing *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1353-54 (Fed. Cir. 2008)).

[26] As a result, Petitioner lacks a viable claim that the second flu vaccine significantly aggravated an existing case of MPA that had already begun (whether or not the earlier vaccine had anything to do with it). *Loving v. Sec'y of Health & Human Servs*., 86 Fed. Cl. 135, 144 (2009) (setting forth prongs required to successfully establish significant

those symptoms or her MPA, Petitioner is left with establishing that the October 2013 dose was enough to cause this form of ANCA-associated vasculitis. In an attempt to provide Petitioner the fullest opportunity possible to prove her case, I offered her the chance to propose an alternative causation theory based solely on the second vaccine dose. Although there is record evidence that supports this alternative causation theory, I nevertheless conclude that Petitioner has not met the preponderant, "more likely than not" test for establishing entitlement, for the reasons set forth below.

1. *Althen* Prong One - Petitioner has proposed that the mechanistic process of molecular mimicry between components of the flu vaccine and self structures could initiate MPA, and Dr. Gershwin relied on the same mechanism when proposing a causation theory limited to Petitioner's 2013 vaccination.[27] Petitioner's Prehearing Submission, dated July 14, 2017, at 9; Gershwin Supp. Rep. at 2-3. As a general matter, such a theory has been successfully offered in *other* Program cases involving molecular mimicry between protein components in a vaccine (here, the flu vaccine) and human peptides, resulting in a cross-reaction where antibodies produced in reaction to the vaccine mistakenly attack self-structures, causing harm.[28] The question is whether this theory is scientifically plausible when invoked in the context of ANCA-associated vasculitis.

The first significant limitation to applying such a mechanism in this case is a lack of reliable medical or scientific literature associating the flu vaccine with MPA. For molecular mimicry to be a credible mechanistic explanation for how the flu vaccine could cause MPA, there should be some evidence that the ANCA antibodies that drive the resulting vasculitis are produced as a result of vaccination – and it is reasonable to require a petitioner to offer some evidence in support of such a contention when evaluating the success of the claimant's prong one showing. *See, e.g., W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1361 (Fed. Cir. 2013) (upholding special master's rejection of molecular mimicry theory where petitioner provided no persuasive evidence establishing that a specific peptide in the vaccine at issue was capable of cross-reacting with specific proteins in the body); *Hunt v. Sec'y of Health & Human Servs.*, 123 Fed. Cl. 509, 523-34 (2015) (discussing *W.C.;* special master properly denied entitlement where petitioner could not

aggravation). It does not appear that Petitioner intended to plead or prove such a claim, however. *See* Petitioner's Prehearing Submission, dated July 14, 2017, at 1, 8, 9-10 (ECF No. 35).

[27] While petitioners need not *prove* a particular mechanism as part of their *Althen* first prong showing, where they propose a theory and attempt to substantiate it, a special master may reasonably evaluate if they have successfully done so, and weigh that showing as part of the overall evidentiary weighing that applies to each *Althen* prong. *Althen*, 418 F.3d at 1278.

[28] The flu vaccine, for example, *has* been associated with a number of autoimmune conditions (like GBS), and has been shown to be able to initiate such a process via the biologic mechanism of molecular mimicry. *See, e.g.*, *Tompkins v. Sec'y of Health & Human Servs.*, No. 10-261V, 2013 WL 3498652, at *22 (Fed. Cl. Spec. Mstr. June 21, 2013) ("[t]he molecular mimicry theory is the one most widely accepted for the agents most frequently accepted as causal"), *mot. for review den'd*, 117 Fed. Cl. 713 (2014).

show the "particular parts" of the vaccine implicated as having cross-reactivity potential under a molecular mimicry/bystander activation theory). Here, however, Dr. Gershwin admittedly could *not* identify the antigenic source in the flu vaccine for this autoimmune process, and cited no medical or scientific literature involving experimentation on this subject. *See* Tr. at 119, 143, 151.

The most scientifically robust evidence that Petitioner offered in connection with this assertion, Jeffs I, proposed only that some form of viral RNA found in certain versions of the flu vaccines could contribute to the development of a particular ANCA antibody. But Dr. Gershwin did not establish that the versions of the flu vaccines evaluated in Jeffs I were comparable to the Fluarix version at issue herein – while admitting he personally did not find this particular theory all that persuasive in any event. Tr. at 143. He also did not show that the antibody at issue in Jeffs I is relevant to MPA – and in fact literature filed in this case suggests it is mainly GPA-associated. *See, e.g.*, Greco at 840; Guillevin at 424. And there is nothing post-Jeffs I in the literature filed in this case suggesting that this theory has found corroboration (indeed, Jeffs I's authors seem to disavow Petitioner's entire theory that the second flu vaccine could cause an acute upswing in the severity of her vasculitis that was brought on in the prior year). Jeffs II at 343, 347-48, 349-50.

Dr. Gershwin offered some general scientific evidence suggesting the flu vaccine has been associated with vasculitis in other regards, but it too fails to link with other elements of his causation theory. *See, e.g.*, Wijngaarden at 238; Spaetgens at 1. Spaetgens, for example, is a case report involving a patient with active glomerulonephritis (a syndrome characterized by rapid renal failure that can accompany ANCA-associated vasculitis) who suffered a relapse following flu vaccine administration. Spaetgens at 1. Spaetgens's authors opined that by activating antigen-presenting cells expressing proteinase-3 (once again, the GPA-associated antibody discussed in Jeffs I), the flu vaccine caused a secondary exacerbation of the existing glomerulonephritis, via nonspecific B and T cell stimulation (akin to bystander activation). *Id*. Spaetgens, however, not only runs counter to other literature filed in this case (e.g., Jeffs II) suggesting that the flu vaccine likely does *not* exacerbate vasculitis, but it also embraces a secondary pathologic mechanism that requires some *initial* autoimmune instigating process that has not been identified as occurring herein. And Dr. Gershwin has been criticized for proposing bystander activation as a primary mechanism for explaining an alleged link between the flu vaccine and vasculitis. *See Schoeberlein v. Sec'y of Health & Human Servs.,* No. 14-697V, 2018 WL 945843 (Fed. Cl. Spec. Mstr. Jan. 11, 2018) (denying entitlement where petitioner alleged a flu/GPA injury).

Petitioner otherwise heavily relies on case reports associating forms of the flu vaccine with different types of vasculitis – but this category of evidence poses problems large and small. It is well recognized that case reports are deserving of *some* evidentiary weight. *Paluck v. Sec'y of Health & Human Servs.*, 104 Fed. Cl. 457, 475 (2012) (noting that although "case reports 'do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary

value' . . . 'the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight'") (quoting *Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650, 668 (2011)). However, substantial authority also notes that case reports are not robust evidence favoring causation (even under the Program's comparatively lenient preponderance evidentiary standard). *W.C. v. Sec'y of Health & Human Servs.*, No. 07-456V, 2011 WL 4537887, at *13 (Fed. Cl. Spec. Mstr. Feb. 22, 2011) ("case reports are generally weak evidence of causation because case reports cannot distinguish a temporal relationship from a causal relationship"), *mot. for review den'd*, 100 Fed. Cl. 440 (2011), *aff'd*, 704 F.3d 1352 (Fed. Cir. 2013); *Caves v. Sec'y of Health & Human Servs.*, No. 07-443V, 2010 WL 5557542, at *14 (Fed. Cl. Spec. Mstr. Nov. 29, 2010) ("case reports do[] not help [petitioners] meet [their] burden of demonstrating a persuasive and reliable theory causally connecting" vaccine to injury), *mot. for review den'd*, 100 Fed. Cl. 119 (2011), *aff'd*, 463 F. App'x 932 (Fed. Cir. 2012); *Shepperson v. Sec'y of Health & Human Servs.*, No. 05-1064V, 2008 WL 2156748, at *11 (Fed. Cl. Spec. Mstr. Apr. 30, 2008) (a single case report is not "sufficiently probative to begin the evidentiary climb to a preponderance"); *Muchnik v. Sec'y of Health & Human Servs.*, No. 90-703V, 1991 WL 217673, at *4 (Fed. Cl. Spec. Mstr. Oct. 10, 1991) ("[f]or petitioner to establish causation in fact by a preponderance of the evidence in any given case requires something more than case reports . . . ."). There is accordingly risk in overreliance on case reports, especially where (as here) other prong one causation proof is ambiguous or lacking.

Beyond such general failings as a category of evidence, the specific case reports at issue are not individually all that helpful to Petitioner. Uji, for example, describes one patient's onset of MPA symptoms seven days following a flu vaccination (a timeframe comparable in certain respects to that of this case). Uji at 892. The explanatory section contained therein, however, is speculative, characterizing the flu vaccine's relationship to MPA as only a "possible association." *Id.* at 895. The remainder of Petitioner's case reports are equally speculative. *See,* e.g., Duggal at 1 (two-patient study noting a "causal role of vaccines in AAV cannot be confirmed with these case reports"); Birk at 290 (three patient "case series cannot reliable differentiate between spontaneous of vaccination triggered vasculitis disease activity"). And it is this kind of case report evidence that larger review articles rely on when mentioning a possible association between the flu vaccine and any form of vasculitis – not independent research. *See, e.g.*, Wijngaarden at 238, 246 (citing three case reports, including Uji). By contrast, other potential causes of ANCA-associated vasculitis discussed in review articles like Wijngaarden have far more facially-valid scientific support. *Id.* at 239-44, 246 (discussing scientific research supporting role of silica or microbial/bacterial infections as playing a causative role in pathogenesis of ANCA-associated disease); *see also* Teng (discussing potential role of Hep B and Hep C infection as trigger for vasculitis generally); Lazarus (discussing causal role of staph or E. coli infection as trigger for ANCA-associated vasculitis).

Such spotty evidence for Petitioner's causation theory could have been imbued with greater heft if an expert with sufficient grounding in ANCA-associated vasculitis, or expertise studying the flu vaccine's capacity to cause an autoimmune injury, had offered opinions in this case, allowing that expertise to bind these less-probative evidentiary items into a greater whole. But Petitioner relied solely on Dr. Gershwin, and he was unable to accomplish this task. Unquestionably Dr. Gershwin was qualified to opine on immunologic matters, and his demonstrated expertise on such fronts required me to take seriously his opinion. But that opinion was ultimately rooted in topics in which he is less well-versed, such as the disease in question – something that was underscored in his unpersuasive insistence (rebutted by Dr. Oddis) that I should ignore distinctions between GPA and MPA. Indeed, even when directed to evaluate causation based solely on the October 2013 vaccine (and thus to take note of my likely finding that Petitioner's earlier symptoms were not consistent with her subsequent diagnosis), he continued to so assert, without also offering any additional evidence that would strengthen his underlying claim about how the flu vaccine might produce MPA-associated antibodies. *See, e.g.*, Gershwin Supp. Rep. at 2-3.[29] At bottom, an expert who has no direct experience studying the pathogenesis of ANCA-associated vasculitis will generally not be overly persuasive in opining on that very subject.

Overall, I do not find that Petitioner's "can cause" evidentiary showing was sufficient. The concept that a vaccine could cause MPA is hardly beyond the pale, and may in the future be more successfully established with some additional scientific or medical evidence providing a more reliable basis for concluding that production of the ANCA antibodies central to this form of vasculitis (rather than to GPA) are promoted by the flu vaccine, or that the immune-stimulating properties of vaccination generally are enough to promote their existence in genetically-susceptible individuals. But Petitioner offered mechanisms that were not reliable, relied on case reports rather than verifiable research or scientifically-derived data, and utilized an expert whose reach exceeded his grasp given the nature of the injury at issue in this case.

2. *Althen* Prongs Two and Three – My finding on the weakness of Petitioner's modified causation theory based only on the October 2013 vaccination makes it unnecessary to discuss at length Petitioner's showings under the other two *Althen* prongs. *See, e.g.*, *Veryzer v. Sec'y of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr.

[29] The low weight I ultimately am assigning to Dr. Gershwin's opinion and testimony was *not* the product of the effectiveness of Dr. Whitton's rebuttal testimony. Dr. Whitton (like Dr. Gershwin, a credentialed expert whose testimony is often of great utility in Program cases) did effectively point out certain deficiencies in Petitioner's theory (for example, that the state of the medical literature does not support a link between the flu vaccine and AAV (relying on Wijngaarden, Teng, and Lazarus). In this case, however, he devoted more time trying (in vain, as discussed below) to establish alternative causes for Petitioner's condition or to explain her ENT symptoms, and like Dr. Gershwin his testimony frequently veered into matters that fell outside his immediate expertise. Because it is ultimately a petitioner's burden to prove causation, however, Dr. Gershwin's inability to unify the disparate items of proof offered into a single persuasive causation theory is what causes me to determine that the first *Althen* prong has not been met.

Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344 (2011). I will nevertheless briefly consider Petitioner's success in establishing each.

First, Ms. Knorr has not successfully demonstrated with preponderant evidence that the October 2013 flu vaccine likely caused any symptom she experienced – although there is considerably more probative evidence on this prong than on the first, "can cause" prong, making it a closer question.[30]

The medical record does establish that a few days after vaccination, Petitioner began to experience flu-like symptoms that she believed were comparable to how she felt after the flu vaccine the year before, followed by an inflammatory process later than same month that eventually led to the onset of her MPA. But this ultimately only establishes a temporal association (vaccine followed by illness), which black letter law in the Vaccine Program establishes as an insufficient basis for the conclusion that the vaccine in fact caused her injury. *See, e.g.*, *Lalonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014) ("a temporal correlation alone is not enough to demonstrate causation"). There is also some treater opinion suggesting the vaccine was a possible trigger for her symptoms, but it seems to be attributable to views expressed to the treater by the Petitioner, rather than to reflect the treater's reasoned view. *See, e.g.*, Ex. 3 at 116, 118. The record references to the flu vaccine as "causing" her MPA are otherwise too conclusory to give much weight, or (like Petitioner's initial theory) rely on associating her earlier ENT symptoms with her subsequently-diagnosed vasculitis. Nevertheless, this kind of evidence supports Petitioner's claim.

In addition, there also appears to be no clearly-identified possible alternative infectious explanation for Petitioner's MPA (other than her chronic ENT symptoms, which could have been viral in nature, although no clear etiology for them has been established either). Tr. at 153 (Dr. Gershwin admitting that he would more closely scrutinize causation (given the facts) in light of any pre-existing viral illness Petitioner may have had during the preceding year). The proposal that an EBV infection caused Ms. Knorr's MPA was certainly not established with preponderant evidence. At best, the record demonstrates that Petitioner experienced some kind of reactivation of an EBV infection that October (something treaters also found significant), but I cannot conclude from the record *what* reactivated it – or more importantly, whether an EBV infection could cause MPA in the first place, given Respondent's reliance on the same weakly probative kind of evidence (case reports) that I critique above in my *Althen* prong one discussion. *See, e.g.*, Xu; Daikeler;

[30] I do not find, however (as discussed below), that Petitioner's *Althen* two showing was sufficiently a "close call" such that it should be decided in her favor based on the Vaccine Program's goals. I am merely stating that (in comparison to prong one) Petitioner made a stronger *Althen* two showing in light of the medical record.

Schned; Ranganath; Yamaguchi; Tr. at 188; *see also* Whitton Rep. at 6-7.[31] Petitioner was, however, more persuasive than Respondent in her argument that her allergy shots were unlikely related to the more severe symptoms she later experienced. *See* Tr. at 175-76, 249.

But the lack of a persuasive alternative explanation for the cause of Petitioner's MPA does not amount to Petitioner having carried her burden of proof. *See, e.g., Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1149-50 (Fed. Cir. 1992) ("evidence showing an absence of other causes does not meet petitioner's affirmative duty to show actual or legal causation"). On the contrary, the record does not allow for the conclusion of something central to a finding in Petitioner's favor: that the October 2013 flu vaccine resulted in the production of the ANCA antibodies necessary for the illness. The many intervening factors, from the EBV reactivation infection to Petitioner's ongoing ENT symptoms, further muddy the waters (even though they have not persuasively been demonstrated to explain her MPA). At best, the record suggests that Petitioner experienced a variety of flu-like symptoms (and/or a continuation of her prior unexplained ENT and hearing problems) within one to two weeks after the second vaccination. Initial testing did not reveal an immediate, existing inflammatory process (given the normal ESR), but hinted at a possible EBV infection reactivation. *See* Ex. 3 at 50. By November 2013 her symptoms had become something that looked like MPA, as subsequent testing (and input by treaters with experience specific to vasculitis) confirmed, with the inflammatory process she was experiencing becoming far more active and alarming. This is generally consistent with the course of MPA – but not corroborative of the conclusion that the MPA was vaccine-caused.

Given the above (and taking into account my prior finding that the Petitioner has not established in this case that the flu vaccine "can cause" MPA), I cannot conclude that the October 2013 flu vaccine caused Petitioner's actual case of MPA. Beyond the temporal association, the record is too ambiguous as to what could have been the source of her illness (an intercurrent infection; the reactivated EBV infection; her chronic otitis media), and there is not enough evidence that would suggest Petitioner had more than a transient reaction to the vaccine.

[31] The parties spent an unnecessary amount of time quibbling over the proper interpretation of the CDC Article and whether Petitioner's EBV titers supported a finding that her infection was ongoing/new, convalescent, or merely an old reactivated infection. *See* Tr. at 217-18, 320-24. Based on the scientific support offered of both experts, the literature suggests that Petitioner's EBV antibody titers most likely were not evidence of an acute (or new) infection, but could reflect a reoccurrence (rendering it an inconclusive trigger) – a point Dr. Whitton ultimately seems to have accepted. *See id.* at 217-18, 320-24; Whitton Post-Hearing Rep. at 2. Dr. Gershwin's arguments that a reactivated infection could not be pathogenic and/or was most likely a product of Petitioner's ongoing vasculitis were not particularly persuasive, but Respondent's larger point about the significance of the EBV infection was itself not carried by sufficient preponderant evidence to conclude it could be an "alternative cause" for her MPA. *See, e.g., Hazelhurst v. Sec'y of Health & Human Servs.*, No. 03-654V, 2009 WL 332306, at *18 (Fed. Cl. Spec. Mstr. Feb. 12, 2009) (discussing evidentiary standards for establishing an alternative cause), *mot. for review den'd*, 88 Fed. Cl. 473 (2009), *aff'd*, 604 F.3d 1343 (Fed. Cir. 2010).

In so finding, although I have acknowledged the existence of evidence favoring Petitioner's position, I do *not* find that this presents a close case that should be resolved in her favor. *See Althen*, 481 F.3d at 1280. Petitioner's weaker showing on the first *Althen* prong simply makes it far more difficult for me to find that the mere temporal association between the October 2013 vaccine and illness onset is proof of a "logical sequence of cause and effect." Without having successfully established how the flu vaccine could cause MPA, I cannot look at this record and conclude it *did so* here – as there is little that can be pointed to from the record establishing that the flu vaccine was causing Petitioner's MPA . *See, e.g.*, *Hunt v. Sec'y of Health & Human Servs.*, No. 12-232V, 2015 WL 1263356, at *23 (Fed. Cl. Spec. Mstr. Feb. 23, 2015) (finding a petitioner who has not established the "can cause" prong, cannot "as a matter of logic" establish the "did cause" prong) (citing *Veryzer v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 344, 352-53 (2011), *aff'd without op.*, 475 F. App'x 765 (Fed. Cir. 2012)), *mot. for rev. den'd*, 123 Fed. Cl. 509 (2015); *see also Caves*, 100 Fed. Cl. at 145 (categorizing *Althen* prong one as "logically antecedent" to *Althen* prong two).

I do, however, find that the third *Althen* prong has been met. As I have determined, Ms. Knorr's hearing and ENT-related symptoms from late 2012 into 2013 are not likely precursor symptoms of her later-diagnosed MPA – rendering this timeframe largely irrelevant. But in response to my invitation, Petitioner proposed alternatively that her symptoms following the second vaccination could alone reasonably be connected to the form of vasculitis she has experienced, given the acute nature of onset which has been successfully demonstrated to be a hallmark of MPA (as confirmed by Dr. Oddis). Tr. at 289; *see* E. Ntatsaki, et al., *Epidemiology of ANCA-Associated Vasculitis*, 36 Rheum. Dis. Clin. N. Am. 447, 453 (2010), filed as Ex. C, Tab 12 (ECF No. 20-7) (dominant feature of MPA is "rapidly progressive renal failure").

The evidence in this case about the actual onset of Petitioner's symptoms accords with the timeframe proposed under Petitioner's theory, and the many case reports she filed (despite their unpersuasive character in establishing causation) involve onset in a time period of days to months after vaccination, consistent with her own experience - although close inspection of those case reports reveals that onset varies depending on the type of vasculitis experienced. *See, e.g.*, Birck at 289-90 (onset of two to three weeks for GPA injury); Duggal at 175 (onset of two days to four weeks for AAV injury); Kwok at E11 (onset of four weeks to two months). The above is sufficient to support the conclusion that Petitioner's MPA began in a medically appropriate timeframe consistent with her causation theory. Of course, the fundamental deficiencies in that same theory mean that the reasonableness of a timeframe based upon it cannot save the claim.

CONCLUSION

Ms. Knorr has credibly established that the health problems she has unquestionably suffered (including but not limited to her MPA) have negatively impacted her daily life, and I have genuine sympathy for her struggles. She has also offered probative evidence in support of her claim – particularly with respect to linking the second flu vaccine dose to her vasculitis. But the preponderant test has not been met. Here, the evidentiary record does not support her contention that any of the flu vaccine doses she received could, or did, cause her form of vasculitis. Petitioner has not established entitlement to a damages award, and therefore I must **DISMISS** her claim.

In the absence of a timely-filed motion for review (see Appendix B to the Rules of the Court), the Clerk shall enter judgment in accordance with this decision.[32]

IT IS SO ORDERED.

/s/ Brian H. Corcoran
Brian H. Corcoran
Special Master

[32] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment by filing a joint notice renouncing their right to seek review.